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From the Sections of Pediatric Neurology and Rehabilitation (Folk Bernadotte Home)
Department of Pediatrics, University Hospital, Uppsala, Sweden

THE DYSEQUILIBRIUM SYNDROME IN CEREBRAL PALSY

Clinical Aspects and Treatment

by

Bengt Hagberg Gunnar Sanner
and Monica Steen

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English text revised
by Maud Marsden

Almqvist & Wiksells
BOKTRYCKERI AKTIEBOLAG
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CHAPTER I

INTRODUCTION

taxic syndromes in cerebral palsy constitute etiologically and clinically heterogeneous o Studies in recent years have revealed a frequency of 12–13 per cent (7 44) In penetrating study Ingram (44) classified the oup into two distinctive main syndromes. without spasticity and ataxic diplegia ith spasticity in the lower extremities. How-er it is also possible to subgroup non-pro- e syndromes of ataxia according to the nating type of motor dysfunction. Thus, are some cases in whom the dominating gn is dyssynergia, i.e. tremor dysmetria and ther signs of disturbed coordination In other the salient feature is a disturbance of and equilibrium i.e dysequilibrium 15 54) In our experience this latter group pon whom we have concentrated our interest y clinical characteristics that justify re this form of cerebral palsy as a special the dysequilibrium syndrome Transl- forms may be found between congenital cerebellar ataxia, e.g. the dyssynergic group, and the dysequilibrium syndrome, but patients in whom the clinical picture is dominated by dysequilibrium show a typical motor development and neurological picture and marked disturbances in their perceptional field. Within the group of stationary cerebellar ataxia, where cases of the dysequilibrium syndrome are usually found, we consider that it is important to recognize this syndrome mainly because of its different prognosis and of the therapeutic approach required

To our knowledge no comprehensive study has been devoted to the syndrome of dysequilibrium. In this supplement we will present our findings and experiences from 13 cases of non-progressive motor disturbances dominated by a defective sense of equilibrium and body position, studied during various developmental stages at the cerebral palsy clinic in Uppsala during the years 1956–1968 and again at a planned follow-up investigation in 1969

CHAPTER II

DEFINITIONS

Considerable difficulties arise when trying to find adequate neurological terms in discussing the different forms of ataxic syndromes within the concept of cerebral palsy The terminology for adult conditions does not always cover the clinical pictures met in development neurology This applies to congenital states (among others) with difficulties in achieving and maintaining an upright posture. It is not surprising that a large number of different names have been used to designate these conditions. In this connection the importance should be stressed of differentiating between the concepts of signs and syndromes ataxia, for example is often used alternatively for designating both a sign and a syndrome

Definition of general terms

The terms and system of classification of the main forms of cerebral palsy are given in Table I and comprise a slight modification of the classification used in Sweden since 1960

Table 1 *The approximate distribution of the different cerebral palsy syndromes in children in 1960 according to the classification mainly used in Sweden*

	%	%
Spastic syndromes		55–60
Hemiplegia	25	
Diplegia	30	
Tetraplegia	5	
Dyskinetic syndromes		25–30
Mainly athetotic	5	
Mainly dystonic	20–25	
Ataxic syndromes		10–15
Congenital ataxia	5–7	
Ataxic diplegia	5–7	

(7) and originally introduced in 1958 by one of the authors (B H.) from a test series in Uppsala

The sign *ataxia* is considered to be present when there is a disturbance of coordination of voluntary movements due to dyssynergia the muscles.

…*ysequilibrium* as a sign, is used to indi… incapability of or pronounced difficulty in maintaining posture and equilibrium, owing to defective postural reflexes.

Concerning the relation between dysequilibrium and ataxia, Mettler & Orioli (63), in their studies of …bnormal movement, conclude· Only two forms of ataxia, …pinal and cerebellar can be distinguished, but it is necessary to differentiate between these two entities …nd, further bet…een them and dysequilibrium. Dysequilibrium and cerebellar ataxia …ften occur together Ataxia in it… strict sense is not evident until movement is attempted, while dysequilibrium mainly is a defect in the system of postural mechanisms.

Truncal ataxia and *truncal tremor* used alternatively mean conditions where the ataxic signs are mainly distributed in the trunk.

We do not use truncal ataxia synonymously with dysequilibrium. In this w… has… found support in Marshall (60), who states regarding disturbances of posture and equilibrium that "truncal ataxia is an unsuitable name in that it suggests that the disability is confined to the trunk while in fact it is equilibrium as a whole which is disturbed" It is true that truncal tremor is regularly encountered in certain developmental stages of cases with dysequilibrium, but it is not obligate.

Ataxic diplegia is considered to be present when spasticity of diplegic distribution is found in addition to ataxia

Definitions of syndromes

For the purpose of this supplement the characteristics of the following two syndromes should be differentiated.

The synd ome of congenital cerebellar ataxia. A non-progressive neurological condition dominated by incoordination of voluntary movements, i.e. signs of dyssynergia such as dysmetria, unsteady gait and marked intention tremor of the upper extremities. Falling occurs with normal compensatory movements of the extremities. The motor development usually starting in a stage of floppiness, is moderately retarded with achievement of independent walking at about 2–5 years of age.

The dysequilibrium syndrome A non-progressive neurological condition dominated throughout childhood by incapability of or *pronounced difficulty in maintaining an upright* body position and in experiencing the position of the body in space, i.e. a lack of *sense of equilibrium* This condition has nothing to do with dysfunction of the vestibular organs. Signs of dyssynergia, such as dysmetria and intention tremor may be present to some extent, but are often obscured for years by the dominant disability The motor development is *severely retarded, independent walking* seldom being achieved before school age

CHAPTER III

EARLIER LITERATURE

The literature concerning congenital ataxia is rather confusing This applies particularly to the terminology Definitions are generally lacking Freud (26 27) was the first to observe

children suspected of representing an ataxic form of congenital cerebral palsy In 1903 Batten (8) described 8 children with congenital cerebellar ataxia or cerebellar diplegia" Marked unsteadiness, incoordination of the limbs and intention tremor dominated the neurological signs. They were slow in their motor development but learned to walk at about 4 years of age These cases of Batten s mainly seem to represent traditional symptomatology of congenital cerebellar ataxia.

In the same year Anton (6) from Austria published a report which probably constituted the first documented description of a case representing a second group His patient, a girl 6½ years old, had never learnt to stand or walk and was unable to maintain equilibrium when put in a standing position The movements of her arms and legs were markedly ataxic, but nothing was said about tremor At autopsy she was found to have among other things, a subtotal cerebellar aplasia, rudimentary corpus striatum and atrophic nuclei of Deiter The pathways between the spinal cord and the cerebellum were completely absent. The next report—often quoted in the literature—is that of Foerster (24) He described 4 cases with der atonisch-astatische Typus der infantilen Cerebrallähmung The main characteristics were extensive hypotonia with pronounced passive mobility of the joints and inability to maintain posture in spite of normal power and mobility when lying down. Incoordination and tremor were observed but did not seem to have dominated the clinical picture All four were mentally retarded. Foerster pointed out that his cases differed markedly from the cases of congenital cerebellar ataxia described by Batten in 1903 In the following years other authors presented cases similar to those of Foerster's but under different headings Clark (18) described patients with infantile cerebro-cerebellar diplegia of the flaccid atonic-astatic type" and Batten & von Wyss (9) presented cases of "the atonic form of cerebral diplegia"

In 1959 van Rossum (74) made a review of Foerster s atonic-astatic syndrome" and added 2 further cases. He summarized the following signs as being typical of the syndrome: pronounced hypotonia, moderate ataxia, astasia-abasia, dysarthria and sometimes mutism the intellectual capacity varied but there was usually mental retardation Characteristically there was a slow improvement of the motor function and intellectual capacity Up to 1959 van Rossum had collected 40 cases considered to have "the atonic-astatic syndrome" but in spite of his statement that an improvement is characteristic, cases of non-congenital, progressive ataxic diseases also are referred to obviously making his series heterogeneous.

Kramer & Vojta (55) on the basis of a study of 179 hypotonic children, discussed the problem of early diagnosis of "kongenitales cerebellares Syndrom" They found 32 children considered to be cases of "kongenitales cerebellares Syndrom" and 44 children with atonisch-astatisches Syndrom" Even though they did not define their "atonisch-astatisches Syndrom it seems likely that they in fact differentiated between the syndrome of congenital cerebellar ataxia and the dysequilibrium syndrome. The authors claimed that it should be possible on clinical grounds to differentiate between the two syndromes in question and also other important states of infantile hypotonia already during the first months of life Obviously these authors are aware of the existence of a syndrome with disturbed balance in addition to the syndrome of congenital cerebellar ataxia.

Many of the cases from the literature classified as belonging to the type described by Foerster including two of Foerster's own original patients, were at the most 3 years old at the last examination. As pointed out by Lund (58) these cases were characterized by a generalized hypotonia without any other neurological signs. In the patients examined at an age above 3 years neurological signs were present in addition to the hypotonia. These were primarily signs of cerebellar ataxia, but there were also cases with athetosis and/or

spasticity Thus, the name Foerster s atonic astatic syndrome" as used in the literature seems to have covered a heterogeneous group the common denominator being a clinical picture of a floppy infant" in the first years of life As the "floppy infant syndrome" embraces a large number of various conditions and as the differential diagnosis of hypotonic forms of abnormalities in infancy and early childhood is extremely difficult, it seems probable to us that many cases have been wrongly classified and thought to represent an astatic syndrome on developmental more than on neurological criteria.

In the existent reports of cases with Foerster's syndrome" a correlation of the symptoms and signs with the chronological, mental and motor development is lacking. This would seem essential in discussions of neurological disorders in infants and children. However even if the cases described as "Foerster s syndrome" constitute a heterogeneous group, a characteristic clinical picture, as last presented by van Rossum (74), is discernible and some of the patients obviously have the same disorder

Lesny (56) used hypotonia as a starting point and presented an investigation of 33 cases with hypotonic forms of cerebral palsy" He found that one third of his cases had ataxia, this being "of the posterior column typo at least as often as ataxia of the cerebellar type" Thus, he perhaps *differentiates between cere bellar ataxia* and the atonic-astatic syndrome which we have called the dysequilibrium syndrome As for his other cases, he found hypotonicity combined with spasticity as well as with extrapyramidal disorders In fact, it is doubtful whether there is any real motivation for designating a special group as pure hypotonic cerebral palsy In the majority of such cases the hypotonia is present as the dominating sign only during the first years of life, i.e it is an expression of the varying functional interrelations in the developing brain In older children, hypotonic cerebral palsy in the absence of other neurological signs probably exists mainly in profoundly mentally retarded children Yannet & Horton (86), in an investigation of hypotonic cerebral palsy in mentally defectives" found besides groups of ataxic and athetotic patients a group with pure hypotonia. These children were obviously at least 3 years of age However the authors also included cases of deteriorating disorders such as Tay Sachs disease Ford (25) in his review of "congenital atonic diplegia" re marks that cases with severe motor disturbances within this group are also profoundly mentally defective In these cases with an ex tremely low intellectual level the mental re tardation is the outstanding clinical feature The associated hypotonia, in our opinion, can scarcely be justified as a basis for forming a special group within the concept of cerebral palsy

From series of cases with ataxic cerebral palsy presented in the literature (44 46, 77), cases with dysequilibrium as the predominant feature cannot be differentiated. In Ingram s original series (44 46) the developmental story and the neurological picture suggest that most of his patients have a predominating congenital cerebellar ataxia Ingram stated in the majority of cases, the most evident manifestation of underlying ataxia was abnormality of the gait rather than gross unsteadiness in the erect position" a statement that is in agreement mainly with congenital cerebellar ataxia *and not with a dysequilibrium syn*drome Recently Ingram (49) has noted that within the group of ataxic cerebral palsy there are cases in whom the failure to develop postural control is striking, whereas limb movements are less obviously incoordinate Further according to the detailed information on motor development given in Ingram s paper some of his patients obviously could be classified as cases of "the dysequilibrium syndrome" However Ingram does not want to regard these children as a special group mainly because he believes in a continuous spectrum from cases with marked cerebellar dyssynergia on the one hand and cases with marked postural disability on the other

In the 32 cases with congenital cerebellar ataxia investigated by Schutt (77), the motor development and clinical findings are in agreement with the syndrome of congenital cerebellar ataxia according to our definitions. Even if cases with predominantly postural dysfunction are included, they cannot be differentiated from the data given.

CHAPTER IV

CLINICAL MATERIAL AND EXAMINATION METHODS

Clinical Material

The clinical material consisted of 13 patients chosen among 545 children with cerebral palsy who had been referred for special neuropaediatric examination to the cerebral palsy clinic in Uppsala during the years 1956–1968. All patients during these years were examined by one of the authors personally (B. H.). The same methods of evaluation and recording and the same classification were used throughout this period. The form of classification and an approximate distribution of cerebral palsy patients in Sweden within the diagnostic groups are presented in Table 1. Nine of the 13 patients of the present study were also evaluated further and treated for periods at the Folke Bernadotte Home, which is a centre for children and adolescents with motor handicaps from the Uppsala region and a part of the Department of Paediatrics in Uppsala. With the exception of one patient, all 13 were living in the hospital region (Fig. 1), which in 1969 had 1.3 million inhabitants.

The primary material comprised 20 patients, but 7 were excluded for the following reasons: Four patients who at an age of 2–3 years were thought to be cases of the dysequilibrium syndrome were found on subsequent examination to have predominantly cerebellar ataxia or to be extreme cases of anomalous late motor development. One patient, in addition to dysequilibrium, also had a dyskinetic form of cerebral palsy with dystonia, as a result of an early encephalitis, and was therefore considered to diverge too greatly from the material as a whole. In another patient the disease was found to have a progressive course and he was thus excluded. Finally, a further patient was not allowed by her parents to take part in the follow-up examination. Three of the 13 children were females and 10 males. The age of the patients at the first examination and at the final follow-up examination, and the total duration of the follow-up period in each case are given in Table 2. During the observation time none of the 13 children showed any neurological deterioration, a fact that was an absolute criterion for their classification into the group of cerebral palsy.

At follow-up examination all 13 patients were seen by two of the authors (G. S. and M. S.) simultaneously.

Methods used at Follow-up Examination

1. *Motor age examinations*

(a) *The motor age test* devised by Johnson et al. (53) has been used at the paediatric clinic in Uppsala since 1953. The components, divided into fine and gross motor tasks, are standardized for the ages 4 months to 6 years. All our patients underwent this test as a part of the follow-up examination. Many of the patients were older than 6 years, but none reached higher than the 4-year level in this test.

(b) *The motor impersistence test* devised by Yule et al. (87) is intended and standardized for the ages 9–10 years. It has been shown that motor impersistence is a developmental phenomenon, related to age, IQ and brain damage.

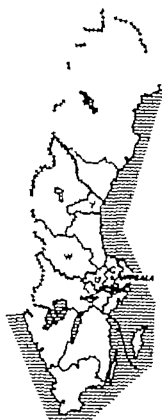


Fig 1 The region covered by the University Hospital of Uppsala.

This test was used for the patients of about 9–10 years of age or older

2 *Neurological examination*

A thorough neurological examination was performed, but with special emphasis placed on the proprioceptive functions Tests of position sense vibration sense, two-point discrimination graphaesthesia and stereognosis thereby following a scheme used by Abercrombie et al. (2) were performed

3 *Ophthalmo-neurological examination*

An ophthalmologist performed an ophthalmoneurological examination in every patient at least once but this was not regularly repeated at the follow-up examination.

4 *Hearing and language*

Pure tone audiography was performed in all 13 patients and in 11 of them the audiograms could be evaluated two of the younger patients were unable to cooperate satisfactorily Three patients (cases 3 6 and 7) underwent *speech audiography*

Eight of our 13 patients were evaluated by speech therapists over several years and the other patients at least once at the time of follow-up At each examination an estimation of the age level of two areas of the language concept was made viz. verbal comprehension representing the afferent functions, and development of speech, representing the efferent functions. The values used for the normal development of language were those presented by Gesell (31)

Table 2. *Basic data for the patients in our series*

Case no	Record no.	Initials	Sex	*Date of birth*	*First examination in Uppsala* Age, years	*Final follow-up examination* Age, years	*Total duration of follow-up period* Years
1	FB 45/63	B-O B		480718	10	21	11
2	1640/59	J N		510801	5 /	17 /	12
3	1290/64	L-O A	3	560527	3 /	13 ³/	10
4	1520/66	E M H		570521	9 /	12 ¹/	3
5	FB 169/69	E Å	5	600507	1 /	9 /	7 ⁴/
6	1877/64	T F		610304	/	8 ¹/ₙ	8 /
7	FB 182/68	T B		610305	3 ⁸/	8 ¹/	4 /
8	498/66	L E		610331	3 /	8	4 /
9	129/67	L H		610602	2 /	7 ⁸/	5 ¹/
10	—	J E		611109	6	8	2
11	1449/63	S H		611222	3 ⁴/	7 ¹/	3 /
12	1945/66	O S		630725	1 /	6	4 /
13	694/69	J Å H		640907	1	4 ¹/	3 /

Paediatric clinic in Uppsala or the Folke Bernadotte Home.

5 *Vestibular function*

To exclude vestibular dysfunction as a main cause of the dysequilibrium, a simple test with rotation in a rotating chair and subsequent observation of the nystagmic reaction was used (19)

6 *Neurophysiological examinations*

(a) *Electroencephalography* had been performed in all patients, but was not included in the follow-up examination if performed adequately during the previous years.

(b) *The motor nerve conduction velocity* in one or both peroneal nerves was determined in 12 patients. In 2 of these patients the ulnar nerves were also examined

(c) *The peripheral sensory nerve conduction time* was determined in 6 patients In 3 other patients the sensory nerve conduction velocity in the peroneal or median nerves was studied

(d) *Electromyography* in muscles of the legs, mostly the short toe extensors, was performed in 10 patients.

(e) *Muscle vibration tests.* Tests with high frequency mechanical muscle vibration were performed in all patients. This test can be used as a diagnostic tool to reveal spasticity and to a certain degree ataxia (38) Furthermore, equilibrium can be influenced by vibration of various trunk and lower limb muscles, the afferents from mechano-receptors in these muscles probably normally participating in the central control of equilibrium (22) In this way we were able to obtain more information on the proprioceptive afferents involved in the maintenance of equilibrium.

7 *X-ray*

X ray of the skull had been performed earlier in 10 patients, whereas encephalograms were obtained at follow-up in 5 patients of this series, and in addition in a younger brother of case 4 with an identical clinical picture, as well as in 3 recently diagnosed patients with the dysequilibrium syndrome not included in this series.

8 *Perception tests*

(a) *Visual perception* To evaluate the visual perception, the Marianne Frostig test (28), used for several years at the Folke Bernadotte Home was performed in 6 patients who were able to cooperate This test covers five areas of visual perception. eye motor coordination, figure-ground perception, form constancy position in space and spatial relationships. The test was primarily standardized on 434 normal children 3–8½ years of age Besides formal testing, information was obtained from repeated observations at play which were especially valuable in those patients who were unable to cooperate in test situations.

(b) *Body schema* To obtain a more objective evaluation of this concept, a test by Bergès & Lézine (13) based on the technique using imitation of gestures, was performed. The test was primarily intended for use on children 3–6 years old, but there are also test items for children 6–10 years old, standardized on 216 subjects However it was not necessary in any of our patients to use the test items for children older than 6 years. In this test it is also possible to estimate the developmental age of *laterali ation*

As a complement to the evaluation of the body schema an analysis of a *Goodenough drawing of a man* was made in 12 cases.

(c) *Auditory perception.* No good standardized tests for analysis of auditory perception exist in Scandinavia. It is possible however to obtain some information by studying the behaviour in "speak–do games" and other sound situations as well as by interpreting the speech and comprehension All of our patients were in this way thoroughly studied by speech therapists either repeatedly through years or at the time of follow up

9 *Intelligence tests*

Performance tests with time limits, such as the Wechsler intelligence scale, could not be used for our patients with their constantly low tempo Therefore, in 9 cases, in spite of their verbal problems we chose to use the Terma

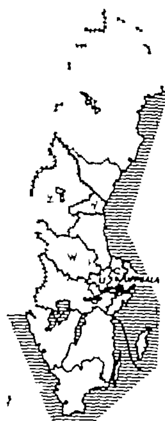


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9	129/67	L H.	♀	610602	2 /	7 /	5 /
10	—	I F	♀	611109	6	8	2
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12	1945/66	O S	♂	630725	1 /	6	4 /
13	694/69	J-Å H.	♂	640907	1	4 /	3 ½

Paediatric clinic in Uppsala or the Folke Bernadotte Home.

Table 3 *Etiological aspects*

Case no.	Sex	Age at follow-up	Order in sibship	Heredity	Age of the mother at delivery	Duration of pregnancy in weeks	Labour and delivery	Birth weight (g)	Neonatal period
1	♂	21	4[illegible]	Maternal uncle of the father mentally retarded	35	36	Normal	3 500	Normal
2	o	18	1/1	—	33	36	Normal	3 [illegible]0	Dullness, feeding problems
3	♂	13	2/2	—	23	35	Asphyxia Foot presentation	900	Dullness, attacks of cyanosis. Tube feeding
4	♀	12	1/3	3/3 showed identical clinical picture at / yrs.	19	34	Normal	3 200	Inactivity
5		9	3/3	First cousin premature, twin with "minimal brain damage	28	36	Prolonged labour	3 350	Inactivity
6	♂	8	3/3	First cousin spastic hemiplegia. First cousin of the mother spastic hemiplegia. First cousin of grandmother "idiot Paternal second cousin epilepsy and spastic hemiplegia	30	33	Normal	980	Normal
7	♂	[illegible]	1/2	Second cousin cerebral palsy	23	40	Threatening intra-uterine asphyxia. Vacuum extraction	3 270	Feeding problems
8	♂	8	1/3	—	18	38	Normal	2 680	Normal
9	♀	8	2/2	Sister epilepsy	29	37	Normal	3 610	Feeding problems
10	♀	8	2/4	4/4 stillborn twin	46	36	Normal	3 420	Very quiet
11	♂	8	2/2	—	20	36	Normal	4 280	Inactivity
12	♂	6	1/3	—	26	38	Syntocinon-induced labour	4 720	Feeding problems
13	♂	5	2/[illegible]	Sister ataxic diplegia	28	35	Normal	3 890	Normal

Case 13 with ataxic diplegia, had a sister similarly affected.

In other families there were abnormalities in distant relatives.

Thus, we can conclude that in case 13 there was evidence of inheritance transmitted through a probably autosomally recessive gene The same is highly suspected in case 4 In a few other cases, especially case 6, there was an over-representation of cerebral palsied or otherwise neurologically affected relatives, perhaps indicating that more complex hereditary factors were at least partially etiologically responsible.

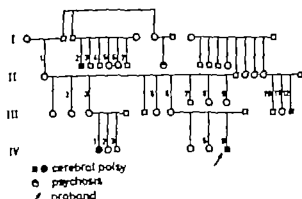


Fig 2 Cerebral palsy in three generations of the family of case 6.

The geographical distribution of the families showed that two families (cases 1 and 11) were descended from the same isolated population, with a high incidence of consanguineous marriages, indicating that the disease could be due to a recessive gene.

Maternal age and number among siblings

The ages of the mothers at the time of the deliveries were evenly distributed. The mean age of the mothers at birth was 26 years, which is not statistically different from that in the general population.

All patients but one had siblings Five patients were first-born Altogether there were 25 siblings, the number of siblings varying between 1 and 7 There were two pairs of twins in different families, and of these one twin (case 10) was stillborn

The distribution according to birth rank and maternal age at the patient s birth gave no support for the possibility that factors connected with the number of pregnancies or the mother s age at the child s birth are of importance for the etiology

Sex incidence birth weight and gestation time

Ten of the 13 cases were boys This ratio differs from that reported by Ingram in his study of congenital ataxia (44) who found a proportion of boys/girls = 4 6 However our material is clinically selected and furthermore small.

All children had a birth weight of over 2 500 g One boy was born 2 weeks after the expected time and had a birth weight of 2 680 g. Of the other patients one boy was born 4 weeks after the expected time and another 3 weeks before, but both had normal birth weights.

Thus prematurity postmaturity or small for date" situations do not seem to be of convincing etiological importance in these cases.

Pregnancies

One mother (case 7) was prescribed Postadoxin® during the first 2 months of gestation because of vomiting. Another (case 10) had mild gastroenteritis in the second month. Otherwise all mothers were reported to have been healthy during their pregnancies no bleeding occurred.

Labour and delivery

Labour and delivery were quite normal in 9 cases. Labour was weak and prolonged in case 5

Case 3 was born in an ambulance, there was a foot presentation and evidence of perinatal asphyxia with longstanding cyanosis and dullness. No further details of this dramatic birth were available

Case 7 was delivered with the assistance of a vacuum extractor because of threatening foetal anoxia. He was slightly cyanotic at birth, but quickly improved when placed in an incubator

The labour in case 12 was induced with an oxytocin drug when the mother had waited 2 weeks longer than expected However the labour delivery and neonatal period were otherwise uneventful.

Thus, in 2 cases there was a history of obvious perinatal asphyxia with a possibility of asphyctic brain damage and in 2 other cases minor perinatal deviations with no significant clinical relevance

Placenta

Unfortunately very little information concerning the state of the placenta was available from

the delivery records. However in case 12 it was noted that the placenta was rich in calcium deposits and in case 6 two small infarctions were found. The latter finding is very frequent and difficult to evaluate The finding in case 12 of heavy calcium deposits suggests a prenatal disturbance

Neonatal period

In case 3 with perinatal asphyxia, inactivity and attacks of cyanosis were noted in the first days of life The child had to be fed by tube. There were also feeding problems in case 7 with threatening foetal anoxia. However cases 2, 4 5 9 10, 11 and 12, in whom there were no signs of perinatal asphyxia, also had feeding problems or showed marked inactivity in the neonatal period, which in these cases were certainly the first symptoms of a prenatally acquired brain abnormality and part of the natural history of the disease

Postnatal disturbances

Case 1 two months old developed severe whooping cough. It is well known that whooping cough in infancy can produce brain damage However in view of this patient s special signs, including cataracts, which will be discussed further later in this supplement, it seems improbable that the whooping cough was of any etiological importance.

In the remaining cases no serious infections or damage to the skull had been noted.

Discussion

There is increasing evidence that prenatal disturbances are more common as a cause of cerebral palsy than was formerly believed. One important aspect in this matter is prenatal asphyctic brain damage (81) Maldevelopment of the brain is another main causative factor For example, Malamud et al. (59), in an autopsy study of 68 mentally retarded cases with cerebral palsy found cerebral malformations in 35% However his cases of ataxia cannot be differentiated.

Ingram (44), in an investigation of children with congenital ataxia, found that about half of the patients with ataxic diplegia or congenital ataxia were born after perfectly normal pregnancies, labours and deliveries. This finding, together with the fact that a rather high proportion showed associated developmental malformations, led to his suggestion that developmental malformation of the brain was probably more important than birth injury

Among cases of congenital ataxia with probably marked dysequilibrium (6, 9 18, 24 74) 6 out of 15 cases had an abnormal perinatal history However from reasons already given, these patients probably constitute a heterogeneous group Therefore no definite conclusions regarding the etiology can be drawn from these reports. One of the patients had a high-arched palate, otherwise no prenatal stigmas or maldevelopments were reported. Van Rossum (74) reported two similarly affected siblings whose parents were first cousins, thus suggesting an autosomally recessive mode of inheritance of the disorder

In some of the reports of siblings with a congenital ataxic syndrome and atrophy" of the granular layer of the cerebellar cortex, the clinical picture is consistent with that encountered in the dysequilibrium syndrome (35 50, 51)

Also in reports of siblings with agenesia of the cerebellar vermis, the clinical picture seems to have been dominated by marked dysequilibrium (37 52)

On the other hand, in an analysis of 41 patients with hypotonic forms of cerebral palsy of whom approximately one-third also had an ataxia, Lesný (56) found no difference regarding the possible causative factors compared with a large unselected material of cerebral palsy

In a recent investigation of identical syndromes of cerebral palsy in the same family Gustavson et al. (36) calculated that a rather high proportion (50%) of cases with congenital ataxia, especially when associated with mental retardation were genetically determined,

Table 4 *Main clinical characteristics*

Stage according to level of gross locomotion	Duration and therapy	Posture and postural reactions	Language
I Floppy inactivity	*3–4 years* Physiotherapy as early as possible	*Muscle tone:* Hypotonia especially of the lower extremities *Head control.* Head lag still at 6 months. 7 mo level reached at 15 mo Righting reactions slowly developing *Sitting balance:* Truncal tremor Good sitting balance acquired between 2 and 4 yrs. Parachute responses and low creeping concomitantly *Held up in standing:* Total flexor pattern of the legs. Sporadic weight bearing	*Comprehension.* Association of certain sounds with human beings and the events they initiate are delayed. Auditory recognition is not followed by visual verification. At age –4 yrs comprehension is still at 1 yr level *Speech:* Very primitive sounds and very poor sign language. Brief and monotone vocalization. Single words
II Cra ling	*2–4 years* *A erage age:* 3–7 yrs *Treatment* Physiotherapy speech therapy	*Muscle tone:* Hypotonia less marked. Rigid legs in standing position *Sitting balance* Normal tilting reactions. Parachute responses prompt and accurate. Frog-sitting. Long-sitting *On hands and knees:* Collapses tilting sideways *Crawling:* On hands and knees with extended arms, lifted feet, side to side movements of the head *Kneeling* Truncal tremor *Standing:* Rigid pillar-like legs, holds on to stationary objects. Frequent collapses. No tilting reaction	*Comprehension.* 18– 4 mo. level. *Understands simple instructions.* Likes give it to me games, points to objects in simple pictures. Likes speak–do games *Speech* 18– 4 mo. level. 6–1 single words, pointing, squeaky sounds. No real jabbering to himself while crawling or in bed
III Standing	*2 3 ears* A erage age: 7–9 yrs *Treatment* Physiotherapy Speech therapy Preschool activities or formal education in special class	*Muscle tone:* Fluctuating. Tendon jerks sometimes quite lively *Kneeling:* Swaying movements *Half-kneeling:* Great imbalance. Position impossible to maintain except when held by the arms *Standing:* Independent for short periods. Legs wide apart. Clown-like backwards falls with stiff legs. No stepping reactions to tilting *Walking:* Tilting reactions improve with the use of crutches	*Comprehension* 4–5 yr level. Pa[illegible] very little attention to instructio[illegible] given to the whole group of chil[illegible] When spoken to more directly a[illegible] to carry out even fairly compl[illegible] commands (depending on IQ). W[illegible] describing relations of objects c[illegible] occasionally be misunderstood *Speech.* 3 yr level. Short ungr[illegible] matical sentences. Makes use of nouns. Can express fundam[illegible] demands. Echolalia. Self-talk du[illegible] play No verbal communication playmates
IV Walking	*Definitive stage* A erage age: >9 yrs *Treatment* Physiotherapy Speech therapy Special education	*Muscle tone:* Tonic stretch reflex. Upright posture better maintained. Execution of willed movements in lower extremities *Kneeling:* Quite steady *Half-kneeling:* Imbalance. Independent rising to upright posture possible *Standing:* Broad-based. Slowly performed stepping reactions. Frequent lurches *Walking:* Dysmetria of steps. Lurches and collapses t any lateral diminution of walking space	*Comprehension:* Mechanical lear[illegible] frequent. Impaired understandin[illegible] the alue of money topography time *Speech:* 4–5 yr level. Makes mut[illegible] in stress situations. Frequent rep[illegible] questions is I don t know Ca[illegible] however verbalize his thoughts. Agrammatism. *Letters and compositions:* Poor s[illegible] ing, fragmentary language, no re[illegible] spirit even in patients with nor[illegible] IQ

Behaviour	Fine motor coordination	Perception and conceptualization
Motor: Total dependence on maternal care during first 2 yrs of life. Pivoting or low creeping *Play:* Absent-minded handling of play material *Domestic:* Has to be fed *Emotional.* Sleeps more, cries less than normal babies. Scared of environmental changes. Introvert. Stereotypical (increases with age)	A. *0–2 yrs supine position* *Manipulation:* Uncontrolled grasp and release *Focusing:* Average age 6–10 mo. *Eye–hand coordination:* Delayed *Grasping for objects:* Average age 6–10 mo B. *2–4 yrs, independent sitting* *Manipulation:* Pronated hand position *Performance:* Overshooting	*Body scheme:* Great poverty of movement. No exploration of lower extremities *Visual.* Pre-perceptual stage prolonged. Visuo-spatial actions disturbed and *retarded* *Auditory:* Stages in development of localization of sounds and the meaning of sounds delayed. Scanty vocal play with very poor motorized component
Motor: Crawling, with head movements reminiscent of a pony. Interrupted by long periods of immobility. Motionless when listening to music and rhythm *Play:* perseveration especially if play material has commensurate characteristics. Sits watching other children play *Domestic:* Messy feeding habits. Verbal communication of toilet needs *Emotional.* Lacking in initiative. More or less autistic	*Manipulation:* Experimenting *Skills:* 18–24 mo. level *Performance:* Disturbed muscle synergy. Kinetic energy reduced. Slow motion. Strength only gained at maximal volitional performance	*Body scheme.* N lateralization. Knows names of main body parts. Drawing at the 18–4 mo level *Visual.* Visuo-spatial and visuo-motor experiences confined mainly to the horizontal plane. Figure-ground relations disturbed *Auditory:* Listening attitude. Very little motor response to auditory stimulation or interest in the localization of sounds
Motor: Needs initial help to start motor activities in upright posture *Play:* Very little interaction with other children except siblings. Make-believe play is rare. Domestic play fairly common *Domestic:* Helps himself in all daily life activities. Pedantic *Emotional:* Frustration may cause violent temper tantrums. Easily excited and uncontrolled. Negativistic. Makes bizarre comments	*Manipulation.* Functional and constructional activities *Skills:* 2–3 yr level *Performance:* Hand position more supinated. Elbows on table or adduction of upper arm whenever precision is needed. Kinetic energy and speed strength reduced	*Body scheme.* No crying or complaints resulting from bumps. Imitation of gestures: 3–4 yr level. Drawing of man dependent on IQ *Visual.* Visuo-spatial and visuo-motor activities carried out in the vertical plane with great effort. Motor control to catch moving objects reduced. Marked visuo-spatial misjudgements *Auditory:* Letter substitutes. Omission of terminal syllables, limited auditory *memory*
Motor: Initial starting reactions inhibited only in new situations or surroundings. Clumsy. Cannot run *Social.* Likes parlour games for two. Enjoys television and radio programmes, tricycle-rides and shopping outings *Domestic:* Pedantic and cooperative *Emotional.* Temper better controlled. Clowning. "I don't mind being alone" attitude	*Manipulation:* Constructional activities *Skills:* Arrest at 4 yr level due to inability to speed up *Performance:* Speed and accuracy of movements impaired. Interval technique makes writing neat. Successful performance with use of tools depends on hardness of material	*Body scheme:* Left–right confusions less common. No coordination of arm movements in the walking pattern *Visual.* Visuo-spatial, visuo-motor and figure-ground confusions and misjudgements frequent in all new learning situations. Misjudgements also when speed is demanded *Auditory:* Central dysperception. Fragmentary language. Writing agnosia

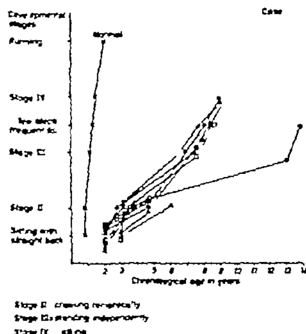


Fig 4 Gross locomotor development in our series compared with normal children.

Pivoting and low creeping do not appear until the age of about 24 months. Usually at the same time the child learns to sit without support the same sitting style which is then retained for several years, is characterized by pronounced kyphosis of the spine and marked outward rotation of the widely parted legs (Fig. 7). Before a good ability to sit is achieved, a coarse truncal tremor when sitting is noticed. Tendon jerks are weak, except for those with associated spasticity Focusing is very de-



Fig 5 "Floppy infant posture in a boy 2 years of age, with all signs of the dysequilibrium syndrome. He still shows the classical signs now at the age of 3) years.

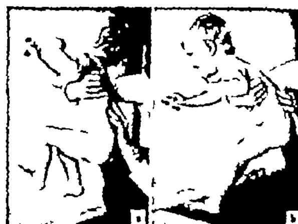


Fig 6 (*a*) Total flexor pattern of the legs when held up, in a boy with the dysequilibrium syndrome (same child as in fig. 5). (*b*) The same boy now more frustrated, with his knees extended and the hips semiflexed.

layed and a convergent squint is almost the rule Babbling is infrequent and only single words are learnt during this stage. An introverted and stereotypical behaviour is charac teristic, adding to the impression of a severely mentally retarded or autistic child.

Treatment Physiotherapy is to be recom mended as it seems to cut down the length of stage I by about a year The treatment should be based on principles of activating the gamma neurons and the intrafusal muscle fibres, the function of which has also bee called the follow-up length servo" (33). Onc the "servomechanism" for controlling afferen discharge is started, however slow and im perfect, and the patient thus acquires the basi prerequisites for reaching a higher moto developmental level, the problems of differ ential diagnosis from other syndromes or hypo tonia and mental subnormality will be reduced The so important mother–child relationshi will also improve when the mother knows ho to handle the delayed development of he child better

Stage II Crawling (Fig 8)

Definition This stage has been named from the natural mode of moving around, i.e. reciprocal crawling on all fours, during a period

when a child is still unable to stand independently or walk The mean duration of this stage was found to be 2–4 years, and the average age for the period 3–7 years.

Clinical picture A less hypotonic child is seen than in stage I and with usually normal tendon jerks. The legs bear weight when the child is held under both arms. He is rather steady when sitting Typically the parachute reaction on backward falling does not function Kneeling is extremely unsteady and is accompanied by coarse tremor in the trunk. Most of the children in our series crawled on all fours with reciprocal movements, arms extended, feet off the ground and with their heads moving up and down and from side to side (Fig. 8). Some children, however crawled by rabbit bouncing or bottom shuffling" as exceptions to the rule

Fine motor coordination. Grasping and manipulating are characterized by a prone position of the hand, and there is disturbance of muscle synergia, with reduced strength. Dysmetria and some intention tremor are regular findings.

Language In this stage only single words are still uttered, and articulation is poor Typically sudden unarticulated high-pitched sounds are produced.

Behaviour The child is very inactive even if other children are playing around. Persever-

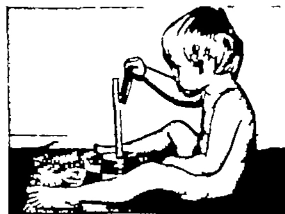


Fig 7 Sitting style, shown by case 9 at 3 years of age, with kyphosis of the spine and widely parted outwardly rotated legs.

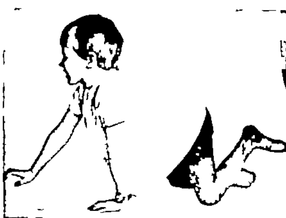


Fig 8 Crawling of a 5½-year-old girl with the dysequilibrium syndrome. Note the "feet up in the air" style.

ation in playing is a regular finding. Cars are placed in neat rows. The impression is that of an autistic and stereotypical child.

Treatment Speech therapy is necessary as a complement to physiotherapy Speech therapy should, in our opinion, stress language training as the children are too young for articulation exercises Preschool activities in very small groups or alone with the teacher are desirable The teacher is recommended to choose activities which will involve the whole body and not only the hands, although manipulation is unsteady and clumsy

Stage III Standing (Fig. 9)

Definition. This is a stage when the child is able to stand up without support, but cannot yet move independently from that position. The mean duration of this stage was 2–3 years in our series. The children were then usually 7–9 years old.

Clinical picture The standing stage is often preceded by a period when the child pulls himself up with the help of furniture or walls, but does not seem able to either sit down or stand independently He may be seen standing with rigid legs, pressing his back against a wall for hours if not helped to get away If one is able to persuade the "no, I don't want to" child to let go from the wall, he will fairly soon learn to stand independently for short periods. When placed in an independent stand



Fig 9 Case 3 at 9 years of age standing characteristically with broad base and raised hands.

ing position, practically all of these children fall over like a felled pine, at first in the direction of the centre of gravity without any compensatory movements. This is a very characteristic sign and distinguishes the clinical picture from all other syndromes of motor dysfunction within the group of cerebral palsy Fig 10 illustrates this typical mode of falling in case 5 at the age of 10½ years (*a*), and in a 7-year-old girl with the dysequilibrium syndrome, not included in this series (*b*).

When independent standing is possible it is characterized by the widely parted legs, the wide-open eyes, the clown-like falls with extended legs incited by turning of the head to one side or tilting or any other form of startle reflex stimulus His stability is upset by stimuli that normally would not have produced any manifest reaction at all The neck-righting reflex is very strong Head turning results in falling over to the side towards which the child is facing.

Bathing in a pool during stages II and III reveals the syndrome very dramatically The legs float around with no control, giving the appearance of astronauts moving in space. The children seem extremely frustrated by the "good-bye feet" experience and get hold of bars and people in panic. Gradually they will gain some control in stage IV

When tilted, no stepping reactions are released. Half kneeling is still very imbalanced and cannot be done independently

Fine motor coordination. When precision is needed, the elbows are held on the table or supported by adduction along the trunk. Slow speed in all movements is characteristic. The developmental age as measured by the "Rochester test" (53) is at the 2–3 year level.

Marked difficulties are apparent when visuo-spatial and visuo-motor activities are carried out in the vertical plane.

Language Short ungrammatical sentences are used exclusively Fundamental demands are expressed in a laconic way

Behaviour Slow pedantic, negativistic and easily frustrated to furiousness. Sometimes bizarre The face is often mask-like with poor mimicry Really good laughs are seldom heard. The child can fall and get severely hurt without crying. The perseverance and pedantry may be observed in drawing (Fig 11).

Treatment Preschool training and group activities also in physiotherapy hand in hand with speech therapy form the ideal approach, as the child's problem is the integration of his sensory inflow to an adequate response. The stimulation must be repetitive and intense, as body reactions will always tend to be a little late in any system employing negative feed-back and are extremely late in our children.

Stage IV Walking

Definition. Walking is defined as the ability to manage independent gait 200 m or more.

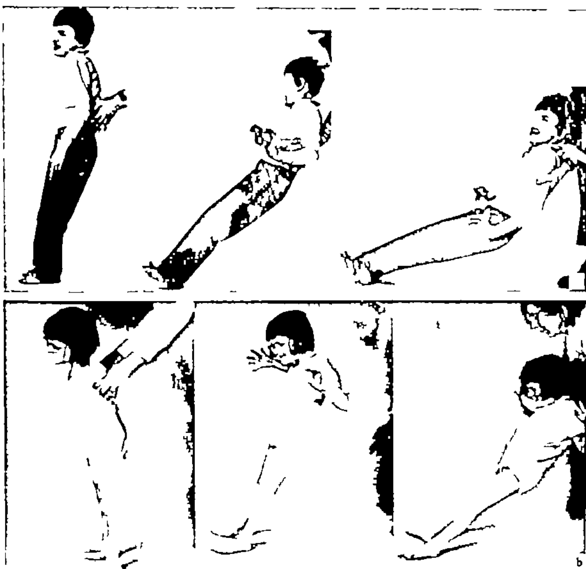


Fig 10 Typical falling without stepping reactions by two patients with the dysequilibrium syndrome. (*a*) Case 5 at the age of 10½ years. (*b*) A girl, not included in this series, at the age of 6½ years.

This is the definitive stage, when the child has acquired the basic motor pattern that he will have to live with as an adult. His gait will, however usually be marked by various compensatory contrivances. Stage IV is usually not reached before the age of 9 years (Fig. 4). Patients with a severe degree of the syndrome probably never reach this stage.

Clinical picture The muscle tone is much more normal and the rigidity of the legs in the upright posture is to some extent under control. The gait is broad-based and the feet are slapped on to the ground with the ball of the foot first, after being lowered in a slow tentative manner He cannot keep in rhythm with the slowest beat for any length of time Dysmetria of steps and lurching and collapsing at any lateral diminution of the walking space were typical of all our patients. Dysmetria was also apparent in a knee-heel test. The interval between the ability to walk alone indoors and the ability to do the same



Fig 9 Case 3 at 9 years of age standing characteristically with broad base and raised hands.

ing position practically all of these children fall over like a felled pine, at first in the direction of the centre of gravity without any compensatory movements. This is a very characteristic sign and distinguishes the clinical picture from all other syndromes of motor dysfunction within the group of cerebral palsy Fig. 10 illustrates this typical mode of falling in case 5 at the age of 10½ years (*a*) and in a 7 year-old girl with the dysequilibrium syndrome not included in this series (*b*).

When independent standing is possible it is characterized by the widely parted legs, the wide-open eyes, the clown-like falls with extended legs incited by turning of the head to one side or tilting or any other form of startle reflex stimulus His stability is upset by stimuli that normally would not have produced any manifest reaction at all. The neck-righting reflex is very strong Head turning results in falling over to the side towards which the child is facing.

Bathing in a pool during stages II and III reveals the syndrome very dramatically The legs float around with no control, giving the appearance of astronauts moving in space. The children seem extremely frustrated by the "good-bye feet experience and get hold of bars and people in panic. Gradually they will gain some control in stage IV

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Fine motor coordination. When precision is needed, the elbows are held on the table or supported by adduction along the trunk. Slow speed in all movements is characteristic. The developmental age as measured by the "Rochester test" (53) is at the 2–3 year level.

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Stage IV Walking

Definition Walking is defined as the abilit to manage independent gait 200 m or more

Table 5 *Results of Rochester motor age test at follow up examination compared with mental age and chronological age*

Stage	Case no.	Chron. age (years)	Mental age (years) (IQ)	Motor age (months) Upper extremities	Lower extremities	Care
Floppy inactivity	13	4 /	Moderately mentally retarded	30	10	At home[a]
	12	6	Moderately mentally retarded	24	10	CP centre
Crawling	11	7 /	3 / (90)	36	12	At home
	10	8	6 / (80)	30	12	CP centre
	5	9 /	3 (40)	36	1	At home
Standing	9	7 /	6 / (87)	36	21	At home[a]
	8	8	8 (100)	36	1	At home[a]
	7	8 /	5 (60)	36	12	At home[a]
	4	12 /	6 (50)	36	12	CP centre
	1	21	8 (54)	45	21	CP centre
Walking	6	8 /	8 (93)	35	1	CP centre
	3	13 /	6 / (50)	45	1	CP centre[b]
	2	17 /	8 / (57)	45		ESN school

[a] Periods of training at the Folke Bernadotte home.
[b] Folke Bernadotte home.

quately This state of dysequilibrium was pronounced in all cases, giving variable effects on the motor function, depending upon the clinical stage of motor development of the child, as described in the previous part of the chapter Thus, in the stage of floppy inac tivity dysequilibrium seemed to be the major factor delaying the capacity for sitting balance, and in supported sitting giving a coarse and unsteady truncal tremor In the beginning of the standing stage, attempts to let go of the child in the standing position immediately resulted in an unprotected and fully uncom pensated fall in the direction where gravitational forces preponderated at that moment. The child would fall full length like a felled pine without bending the knees or putting out his legs, elbows flexed, dorsiflexed hands.

When blindfolded, the child in the standing or walking stage became much more imbalanced, a finding which is also true how ever for all types of congenital ataxia.

In addition to the dysequilibrium, all of our 13 patients had minor signs of dyssynergia as a second component, i.e slight intention tremor dysmetria of the arms and legs and dysdiadochokinesia. This component became more evident in later stages, when the dysequilibrium had become partly compensated, allowing walking and other more complex active movements.

The *third* important neurological component of the syndrome was flaccid weakness, not due to any real pareses or atrophy but more connected with the degree of hypotonia. This was always marked during early years, giving the pronounced floppiness.

When seen at follow-up examination, pa tients in the recumbent position and less than 13 years old, with the exception of cases 9 and 13 were still hypotonic especially in the lower parts of the body However patients in stage III when standing, showed, in contrast, a marked posturally dependent hypertonia of the legs due to the exaggerated positive supporting reactions. The generalized hypotonia at rest gradually diminished with age up to adulthood, when it was greatly reduced or had completely disappeared.

Hemiplegic syndromes were not met in any

of the patients There were slight signs of spasticity in the legs in cases 2, 9 and 13 In case 2 these were only observed as ankle clonus and spontaneous patellar clonus but with flexor plantar response and in cases 9 and 13 as ankle clonus, extensor plantar signs and slightly hypertonic legs. In the other 10 patients the tendon reflexes were normal or weak and the plantar responses were flexor

Dyskinesia was looked for in all cases, but none of the patients showed any evident athetosis. However slight hyperkinetic move ments were observed in two children during excessive laughter (cases 2 and 12)

A sixth nerve palsy was found in cases 1 5 and 13 and case 11 showed slight ptosis bilaterally

Two of the patients had convulsions. Case 5 had psychomotor epilepsy and case 9 was re ported by her mother to have had convulsive episodes when watching television

With regard to pain sense all patients re acted normally to pin pricking. The sense of touch was more difficult to evaluate, but was considered normal in the 9 patients who could be tested adequately The proprioceptive som atic senses and associated functions could not be evaluated in all children because of a lacking ability of cooperation or understanding in some cases A normal position sense was found in 11 patients who were able to cooper ate The vibration sense, tested with a tuning fork, was normal in the 12 children whom it was possible to evaluate. A two-point discrimination test, performed on the back of the hand, could be done in 7 cases with normal re sults. However threshold values were not sought. A test for graphaesthesia on the sole was carried out in 5 cases with numbers and in 4 cases with discrimination of a circle, triangle and square all with normal results. Stereognosis was normal in the 12 patients who could be evaluated

3 *Ophthalmological findings*

Cataracts. Cases 1 4 and 8 had bilateral cat aracts, which had been operated on Con cerning case 8, we know that the cataract first developed when the boy was 4 years of age, since earlier examination of the eyes had given normal results. Case 1 was operated on at the age of 6 years and, according to his mother his vision had deteriorated one year before The information about case 4 was not sufficient for us to decide whether the cataract was congenital or not. It was operated on when she was 3 years of age

Eye-muscle palsy As already mentioned, cases 1 5 and 10 had a sixth nerve palsy

Squint Six patients (cases 3 5 7 8, 10 and 11) had an alternating convergent squint and all the other patients had difficulties with coordination of their eye movements when tired.

Nystagmus No nystagmus was found, except on extreme lateral gaze In case 4 operated on for cataract, nystagmoid oscillating move ments were noted.

Ocular dysmetria. When looking at an ec centric point on one side and then quickly transferring their gaze to the midline, some of the patients exhibited overshooting and pendular movements.

No changes in the ocular fundi were found.

Flutterlike oscillations. On fixation for a long time a regular finding in our patients was that the fixation was interrupted by oscil lations of the eyes, causing blurring of the vision for a short while. This phenomenon was noticed especially by the teachers in the reading situation

4 *Hearing and language*

Pure-tone audiogram. Two of the patients were unable to cooperate The other patients showed normal hearing throughout the whole tone scale, except for cases 5 and 9 who had slight and moderate high-frequency defects, respec tively

Speech audiometry The 3 patients examined showed similar results. It was reported that for both ears the words were reproduced with 100% discrimination However the words were reproduced so badly that it was neces-

sary to know which test words had been used before it could be decided whether the patient had heard and understood the words.

Language The language in 11 cases showed a very similar developmental delay Cases 8 and 13 did not exhibit the same kind of total loss of verbalization during the first 4 years of life, although their use of language was delayed. Later they also started to communicate within normal time limits.

In the other 11 children there was impairment even in babbling and the first 4 years were practically silent In the second and third stage of motor development, usually between the ages of 5 and 10 years, the ability of verbal communication had reached the normal standard of 2–3 years of age At this stage echolalia had also developed. In the fourth stage at an age of over 10 years, the language was characterized by poor articulation with primitive sentences and frequent omission of terminal syllables, i.e. a telegrammatic style resembling that of primitive natives trying to use a foreign language.

The speech development and the development of verbal comprehension in those patients examined at least twice during the years are illustrated in Fig. 12. The situation in this respect in all patients at the follow-up examination is shown in Table 6

The development of verbal comprehension, especially was found to be correlated to the intellectual level cases 6 8 and 9 for example all lay within or just below the normal intellectual limits, and also showed the best results in the verbal comprehension test. Two patients (cases 8 and 13) had better articulation than language ability

Perseveration was frequent in cases 2, 3 and 10 but the rest of the patients also showed some tendency Prepositions were frequently omitted. Verbs were often used only in the infinitive. The phonation was abnormal. Loud screams for no reason at all were common even in younger children The voice became loud and squeaky when they were going to say something.

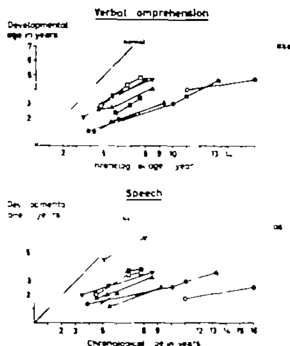


Fig 12 Language development in 9 cases examined at least twice.

5 Vestibular function

Rotation test None of the patients showed any abnormal reaction, the duration of the nystagmus lasting at the most 35 seconds. In 4 patients an otoneurological examination by a specialist had been performed, and no vestibular abnormalities were revealed.

6. Neurophysiological investigations

(a) *Electroencephalography* Ten patients had a normal EEG In cases 5 and 8 there were episodes of epileptogenic activity and case 12 showed abnormally slow activity

(b) *Motor nerve conduction velocity* Normal values were found in 12 cases studied (Table 7)

(c) *Sensory nerve conduction time or velocity* Nine cases were examined all with normal results (Table 7)

(d) *Electromyography* In 7 cases normal electromyographic recordings were obtained In case 1 an increased number of small thin and often split motor unit potentials was seen in several muscles. In case 5 there was a prob-

Table 6. *Language level in individual patients at follow up examination compared with mental age and chronological age*

Stage	Case no.	Chron. age (years)	Mental age (years)	Developmental level in years of verbal comprehension	Developmental level in years of speech	Care
Floppy inactivity	13	4 /	Moderately mentally retarded	3–4	5	At home[a]
	12	6	Moderately mentally retarded	2	2	CP centre
Crawling	11	7 /	3 /	3–4	3–4	At home
	10	8	6 /	4–5	3–4	CP centre
	5	9 /	3 /	3	–3	At home
Standing	9	7 /	6 /	4–5	3–4	At home[a]
	8	8	8	4–5	6	At home[a]
	7	8 /	5	4	3–4	At home[a]
	4	12 /	6	4–5	3–4	CP centre
	1	21	8	6–7	3–4	CP centre
Walking	6	8 /	8	4–5	3–4	CP centre[b]
	3	13 /	6 /	4–5	3–4	CP centre[b]
	2	17 /	8 /	6–7	5–6	ESN school

[a] Periods of training at the Folke Bernadotte home.
[b] Folke Bernadotte home.

able slight lack of motor units, indicating peripheral nerve involvement However the patient was difficult to examine The motor and sensory nerve conduction velocities in both these cases were normal.

(e) *Vibration test* Cases 9 and 13 with clinically manifest spasticity exhibited very strong vibration reflexes. In the other children the tonic vibration reflexes were rather weak. Vibration on the flexor muscles of the fingers in 7 cases (nos 2, 3 6, 8 9 10 and 11) provoked choreo-athetoid movements of the fingers.

During standing, vibration on the Achilles tendons resulted in a normal reaction, i.e. backward falling, but the vibration induced falling reactions were notably weaker than is seen in normal persons.

7 *X-ray examination*

Of the 13 patients, 10 underwent X-ray examination of the skull, and all showed normal

Table 7 *Results of nerve conduction studies in our series*

Case no.	1	2	3	4	5	6	7	8	9	10	11	12	13
Motor nerve conduction velocity (M/s.), peroneal nerve (dx.)	56	45	51	52	62	55	49	58	—	51	61	75	52
Sensory nerve conduction time (s./2nd digit wrist)	51 } 67[b] }	2 5	68[b]	2.8	2.5	57[a]	—	—	—	2.3–2.8	3.8	2.4	

[a] Sensory nerve conduction velocity right peroneal nerve.
[b] Sensory nerve conduction velocity median nerve.



Fig. 13 Encephalogram of case 6 (lateral tomogram of the posterior fossa). The vermis cistern (*1*) and the fourth ventricles (*2*) are enlarged

results. In 5 of these 10 encephalography was also performed. In 2 of these cases (cases 10 and 12) the X-ray findings were considered normal, with the exception of a slight enlargement of the lateral ventricles of the left side in case 12.

In cases 3 and 6 (Fig. 13) the vermis cistern was enlarged, indicating a small cerebellar vermis. The encephalogram in case 5 (Fig. 14) also showed an enlarged vermis cistern, and in addition a very large cisterna magna, indicating abnormally small cerebellar hemispheres. Apart from those cerebellar abnormalities, in case 3 there was slight enlargement of the lateral and third ventricles. In case 5 the lateral ventricles and the fourth ventricle were enlarged, whereas in case 6 a wide fourth ventricle was the only ventricular abnormality.

The results of the encephalographies in these patients and 4 other dysequilibric patients not included in the present series are discussed on page 34

8. *Perception studies*

(a) *Visual perception.* At follow-up examination cases 5, 7, 11, 12 and 13 were unable to complete any scorable tasks in the Marianne Frostig test. Except for case 13, who was in stage I, they were in the crawling stage. Case 8 refused to cooperate, perhaps because he had just been operated on for cataracts. Case 4 was only able to concentrate on a few of the subtests.

The results of the Marianne Frostig test in the rest of our patients are presented in Table 8. Except for case 9 and to some extent case 2, in individual cases and different subtests the scores, when correlated to the chronological age, were generally low. However when correlated to the mental age the results were much better, except in subtest IV (position in space) and partly in subtest I (eye–hand coordination). These results will be discussed in a later part of the paper.

Visual perception is normally a visuo-motor interaction. "A child sees what he does" (32). As formal testing often was not possible during the first two stages in our series, the level of visual perception had to be assessed by informal testing and close observations. What is actually being assessed is the child's visuo-perceptual activity or in many cases the



Fig 14 Encephalogram of case 5 (lateral tomogram of the posterior fossa). The vermis cistern (*1*), the fourth ventricle (2) and cisterna magna (*3*) are enlarged.

child s non-activity as compared with known behavioural responses in normal babies and children.

Just as the children in our series were slow in responding to auditory stimuli when they were babies they were retarded in their response to visual stimuli by new behaviour patterns and imitation. The first social response to visual perception the smile, was very delayed in all our cases. Grasping from the supine position was also abnormally retarded, the average age for the commencement of this action being about 6 months

In the stage of floppy inactivity there is

Table 8 *Results of the Marianne Frostig test of visual perception at follow-up examination*

Case no.	Chronological age (years)	Mental age (years)	Subtests, score/age equivalent I	II	III	IV	V
1	21 /	8	18/8 /	7/6 /	10/7 /	6/6 /	7/9 /
2	18 /	8 /	16/7 /	10/10 +	10/7 /	8/10 +	8/10 +
3	13 /	6 /	22/10 +	7/6 /	8/6 /	1/3 /	6/7 /
6	8 /	8	11/5 /	9/9 /	7/6 /	6/6 /	6/7 /
9	8 /	7 /	13/6 /	10/10 +	17/10 +	8/10 +	7/9 /
10	8	6 /	13/6 /	6/6	10/7 /	-/4	2/5 /

Subtest
I – Eye-motor coordination
II – Figure-ground
III – Form constancy
IV – Position in space
V – Spatial relations

very little true visuo-motor interaction. Later this lack of experience in the connection between visual impression and performance makes the children poor in activities dependent upon good eye–hand coordination and ability to learn movements by watching. In gross movements this applies, for example to throwing and catching balls, jumping and climbing. In finer movements it interferes with their learning to use a pencil, to cut with scissors, copy figures and patterns, to draw and later to understand maps and two-dimensional patterns for three-dimensional tasks.

The children's ability to recognize details, forms, differences and sameness is above their ability to reproduce geometrical forms graphically. At school the dysequilibric child finds it difficult to estimate the size of his letters and figures as compared with those of his teacher. He writes with an uneven pressure which makes his writing easy to distinguish from others (Fig. 15).

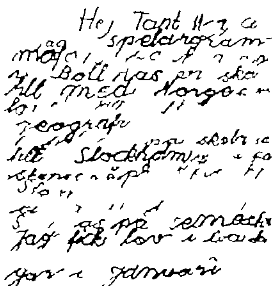


Fig 15 L. ter r ry case at 18 years age, showing markedly u pressure f the pencil.

Left–right confusions occur but are usually compensated for by visual and verbal associations. The non-sliding ruler is a necessary tool for producing even the most simple geometrical forms. These children are slow learners in reading and writing but specific reading and writing difficulties in the strict sense are not characteristic. The deficiency in their ability to fix their gaze, however causes interruption of their reading at intervals.

(b) The *body schema* was in all cases very late developing, according to the imitation of gestures test. None of the children reached higher than the 4-year level, and most of them were even more handicapped in this respect, as shown by Table 9. Accordingly there was a generally slow development of left–right discrimination (Table 9). The oldest patients reached maximum levels of 6 years.

Drawing of a man was generally performed badly (Table 9) and typically the legs were drawn small and incomplete. Drawings by one patient (case 3) at 13 years of age are shown in Fig. 16.

(c) *Auditory perception.* The younger patients, especially during the first stage showed an inability to discriminate foreground and background sounds. Auditory stimulation gave an abnormal response, instead of the normal production of different behaviour patterns or imitation. The voice was characteristically monotonous and badly modulated, and young patients, especially would produce sudden loud screams. Typically the dysequilibric child did not like loud, intense or unexpected sounds and often was seen holding his hands against his ears in situations that would not bother a normal child unduly. The children were usually unable to distinguish between a biting tone and an ordinary voice. Their ability to imitate different pitches was very poor.

In educational work auditory learning was very difficult, the dysequilibric child needing 3–4 times as much repetition as normal children. These observations were considered to indicate a centrally defective mode of dealing with incoming auditory impulses, in spite of normal tone hearing, i.e. an aphasic condition.

Within the concept of aphasia, auditory memory has been considered to be an important part (62).

In an attempt to analyse the different parts



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			I	II	III	IV	V
1	21	8	18/8	7/6	10/7	6/6	7/9
2	18	8	16/7	10/10+	10/7	8/10+	8/10+
3	13	6	22/10+	7/6	8/6	1/3	6/7
6	8	8	11/5	9/9	7/6	6/6	6/7
9	8	7	13/6	10/10+	17/10+	8/10+	7/9
10	8	6	13/6	6/6	10/7	-/4	2/5

Subtest
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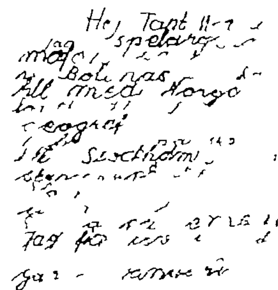


Fig 15 [illegible] showing marked [illegible] pencil

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Within the concept of aphasia, auditory memory has been considered to be an important part (62)

In an attempt to analyse the different parts

Table 9 *Developmental level of body image conception compared with mental age and chronological age at follow-up examination*

Stage	Case no.	Chron. age (years)	Mental age (years)	Developmental level in years of: Pointing to body parts	Drawing of a man	Left right concept	Imitation ability
Floppy inactivity	13	4 /	Moderately mentally retarded	3	–	–	
Crawling	1	4 ¹/	Moderately mentally retarded	– /	2	2	
	11	7 /₁	3 /	3	2 /	3	3
	10	7 /	6	5	4	5 ¹/	3
	5	9	3 /	3	–	3	
Standing	9	7 /	6 /	6	5	5 /₁	4
	8	8	8	6		6	4
	7	8 /₁	5	4	4	3	3
	4	9 /	4 /	5	5	5 /	3
	1	1	8	6	5	6	3
Walking	6	8 /	8	6	5	5 /₁	3
	3	13 /	6 /	6	7	5 /	4
	–	17 /	8 /	6	5	6	4

At earlier examination.
Refused.

of auditory memory the following characteristics were observed in our patients: (i) *Defective memory span*. they were unable to deal with auditory stimuli applied in too rapid succession. (ii) *Defective memory for sequence* syntax errors were regularly encountered. (iii) *Defective patterning of stress and inflection* typically a squeaky often loud and poorly modulated voice was heard. In this connexion rhythm is also interrelated, and our patients had an extremely bad sense of rhythm, also when talking (iv) *Defective patterning of phonetic detail* omitting of terminal syllables was typical.

Thus, our cases seemed to fulfil the criteria of a defective auditory memory

9 *Intelligence tests*

Two patients were found to be within normal limits and 2 just below normal. The other 9 patients were moderately mentally retarded (on an educable level) During the testing procedure, problems generally arose that could have disturbed the results, such as fine motor



Fig 16 Three drawings by case 3 at 12 years of age, drawn on the same day From the left. ( ) Ordinary Good-enough drawing of a man. (*b*) After some further instructions. (*c*) After instructions and after looking at himself in a mirror

disabilities and a low power of concentration The results in the individual patients, given in IQ figures, are shown in Table 5 When more than one test was used, the highest score has been given.

10 Metabolic screening

Seven patients underwent metabolic screening of the urine, as described previously and in all cases the findings were normal.

D *Discussion of Own Series of Patients*

This series of patients showed a very peculiar and characteristic disturbance of the motor development and a distinct neurological syndrome The main neurological defect was a marked disorder of the postural function and hence a disturbed equilibrium Signs of dys synergia, predominantly tremor and dysmetria, were present to a minor extent in all cases. Slight signs of spasticity in the lower extremi ties were encountered, but only in 3 patients. Mental retardation was common but not con stant. Autistic traits and behavioral deviations were often added to the picture Visual and auditory perception were considerably defec tive, constituting a dominant component in the handicap syndrome The development of language was markedly delayed, mainly due to a defective auditory memory

Dyskinesia was not a characteristic sign in our patients. In fact, none of the patients displayed any hyperkinesia at the routine neurological examination However during excessive laughter 2 patients (cases 2 and 12) exhibited athetoid movements of the face The athetoid movements of the face found in a few of our patients have been interpreted as postural reac tions of the facial muscles in the struggle to keep balance during this very exaggerated laughter which engages the whole body (61) One of these 2 patients with spontaneous athetoid traits, as well as 6 others of the series, showed hyperkinetic movements of the fingers on vibration of the digital flexor muscles. Vibration is known to provoke hyperkinetic movements, and in some of our patients these findings were probably indications of slight extrapyramidal dyskinetic involvement.

We found no sensory components of somatognostic disturbances Normal somatognostic senses have been considered to be the rule in all syndromes of cerebral palsy except for spastic hemiplegia (2) although with a refined technique deviations have been revealed (85) However with the methods used, proprioceptive stimuli seemed to be transmitted and re ceived normally in our series. This is also supported by the results of the vibration test during standing The fact that the reactions to vibration were qualitatively normal but quantitativel decreased is most likely a result of a defecti e central integration, although this cannot b pro ed at present (22) No investiga tions appear to ha been made on the falling reactions induced by vibration in cases with a faulty balance. It is therefore impossible at present, to state on the basis of vibration tests, whether the proprioceptive afferents are functioning normally all the way up to the centres of equilibration in the brain.

The postural response of the legs when the child is held in the vertical position, resulting in flexed hips and extended knees (Fig 6) was found regularly in the first stages of our pa tients, and this was especially pronounced when the child was frustrated. This sign was probably first noticed by Foerster (24) and has sometimes been called Foerster's sign" and has been considered typical in cases of atonic diplegia" Ford (25) pointed out that the presence of this sign (which he called Clarke s sign) in cases of "atonic diplegia could rule out a diagnosis of *amyotonia congenita*. However the same sign has also been noticed in cases of dissociated motor development" (40), in "shufflers" (72) and in normal infants (68) It seems as if this postural reflex pattern rather is an unspecific sign, dependent on the stage of motor development. It occurs in the dysequilibrium children in stages I and II, and in the physiological stage of astasia-abasia in normal infants. In normal infants at

this stage, the usual response to vertical suspension is a total flexor pattern of the legs, but when the child is frustrated the knees become extended. It is not surprising that children with the dysequilibrium syndrome pronounced cerebellar ataxia or "dissociated motor devel opment" always become frustrated when they are held up and lose the safety of the floor as a point of reference the resulting reflex mechanism being this frustration postural re flex of the legs.

By clinical and neurophysiological means we have tried to exclude disorders outside the CNS, such as myopathies and peripheral nerve lesions, in our patients. No clinical signs of peripheral nerve involvement were found. This was supported by the findings of normal motor and sensory nerve conduction velocity rates in all patients examined (Table 7) In 8 cases we obtained normal electromyographic record ings. However both in case 1 and case 5 there were changes with sparse split motor unit potentials, the significance of which is uncertain Similar pathological changes are always seen in patients with myopathies. How ever for other reasons myopathy can hardly explain the clinical picture in these patients It is interesting to note that in a few patients with the Marinesco-Sjögren syndrome, electromyographic changes similar to those found in myogenic disorders have been found (5 4) Our case 1 who also had cataracts and mental retardation, may be classified as a case of this syndrome. In his study of hypotonic cerebral palsy Lesný (56) points out that "electromyographic findings are more abnormal in hypotonic cerebral palsy than in any other type" Also Lesný's patients are de scribed as having the same type of changes as in our two abnormal cases. It might be possible that these changes are centrally induced.

Lesný (56) in his series of cases with hypotonic cerebral palsy found 35 abnormal elec troencephalographic recordings among 40 patients examined. In our series only 3 out of 13 patients showed abnormal electroencephalograms. These contrasting results may indicate that our series is not comparable with Lesný's more heterogeneous material.

Pneumoencephalographic studies including tomography revealed heterogeneous findings, the main abnormalities were found in the posterior fossa (Table 10)

Regarding the cerebellum, two or perhaps three main groups could be distinguished in cases 10 and 12—the first group—the ence phalograms revealed no gross abnormalities of the cerebellum. These 2 cases may represent the group of dysequilibric patients where the pathogenetic background can be explained from brain defects on the cellular level. The existence of such a group is proved by the autopsy findings in case 13 and his sister the latter not included in this series, with an iden tical clinical picture including cellular dysplasia in various parts of the cerebral cortex as wel as in the Purkinje layer of the cerebellum o the girl.

A second group represented by cases 3, 5 6 and another patient appearing later (R J) had as a common denominator an enlarged vermis cistern, indicating a small cerebellar vermis Whether the vermis was small because of primary hypoplasia or because of secondary atrophy is, of course, not possible to decide from the X-ray studies. In our case 5 and case R. J., in addition to the large vermis cistern a large cisterna magna was found. This finding as concerns the lateral parts of the cistern may indicate small cerebellar hemispheres, but concerning the middle parts may also represent diminution of the lower part of the vermis.

In this group cases 5 and 6 and R. J also had an enlargement of the fourth ventricle, a further indication of a small vermis.

Finally 3 further patients with the dysequilibrium syndrome, not included in this series, seemed to show encephalographic results similar in character as regards the cerebellum. Of these 3 patients, one (N-O H) was the younger brother of case 4 (one of the three patients in our series with cataracts), but had no cataracts himself another patient (E W)

Table 10 *Pneumoencephalographic findings in 9 patients with the dysequilibrium syndrome*

Case no	Infratentorial region				Supratentorial region	
	Vermis cistern	Cisterna magna	Fourth ventricle	Cisterna pontis	Lateral ventricles	Third ven[illegible]
10	—	—	—	—	—	—
12	—	—	—	—	Slight enlargement of left [illegible]	—
6	Large	—	Large	—	—	—
3	Large	—	—	—	Slightly [illegible]	S[illegible]
5	Large	Large	Large	—	Slightly enlarged	—
R. J	Large	Large	Large	Large	—	—
A. H.	?	Large	Large	Large	Slight enlargement of left side	
N.-O. H.	?	Large	Large	Large	Slightly enlarged	Slightly enlarged
E. W	?	Large	—	Large	—	—

Patients diagnosed 1968–71 and not included in the present series.

had cataracts, and the third patient (A. H.) had no cataracts.

All three had an enlarged cisterna magna and a large cisterna pontis. In none of these cases was the vermis cistern visualized, and it is therefore impossible to state whether it was of normal size or enlarged in these patients. However in two of them (A. H. and N.-O. H.) the fourth ventricle was found to be large, possibly indicating that parts of the vermis were small. On the basis of the examinations performed it cannot be stated with certainty whether these 3 patients should belong to the second group or constitute a third variant.

With regard to the cerebrum, in 4 out of 9 patients (cases 6 and 10 R. J and E. W) no gross abnormalities were revealed. In the remaining 5 patients (cases 3 5 12, A. H. and N.-O. H.) slight or moderate enlargement of the whole or parts of the lateral ventricles was found. The third ventricle was enlarged in case 3 and N.-O. H. These cerebral abnormalities were not associated with any particular cerebellar defect.

To summarize, our experience from encephalographies suggests that the clinical picture of a typical dysequilibrium syndrome can be associated with different cerebral defects, mainly of the cerebellum but also of other parts of the brain One interesting point, perhaps a common denominator in many of these cases, seems to be a defective cerebellar vermis. In a large series of cases with ataxic cerebral palsy defects of different parts of the brain were observed in encephalographic studies (49) These abnormalities included cortical atrophy schizencephaly and small cerebellar hemispheres. Lesny (56) made a study of patients with a uniform clinical picture, which he called "symmetrical cerebellar hypogenesis" It is interesting to note that in these cases, which we certainly should have classified as cases of "the syndrome of congenital cerebellar ataxia" he found small cerebellar hemispheres on encephalography in 19 out of 28 children However in none of these cases was a small cerebellar vermis revealed.

It therefore seems plausible that one common denominator in dysequilibric patients may be a *defectively functioning cerebellar vermis*. The vermis was abnormally small in at least 4 of our 9 patients with the dysequilibrium syndrome who underwent encephalography The encephalographic findings in a larger series of cases under investigation at present, with different forms of ataxic cerebral palsy

may give better understanding of differentiat ing anatomical defects in the two neurological syndromes in question (14)

From our experience from this series, as well as from patients appearing later it is thus evident that developmental defects of the cere bellum, particularly the vermis, are with all probability of major importance as explana tions for the dysfunction of equilibrium To explain the rest of the multifacetted dysequili brium syndrome, especially in those cases with mental retardation, other parts of the brain must be considered It is interesting to note that in our encephalographic series those pa tients in whom abnormalities of the lateral ventricles were found (5/9) were all considered to be mentally retarded, whilst in the other group with normal lateral ventricles 3 out of 4 patients were mentally normal or only slightly subnormal.

All our patients, except two were extremely retarded in their *language development* and, when it did develop there was still a typical linguistic impairment with nonverbality in fantile articulation and agrammatism Mentally retarded children are also considerably delayed in their language development. However in our series there were no marked dif ferences in onset of the use of language be tween mentally retarded and mentally normal children. This observation differs from the findings of Ingram (47) who states regarding speech defects in children suffering from congenital cerebellar ataxia that "retardation of speech development is usually proportional to the degree of mental impairment" Ingram (47) also reports 3 children with congenital cere bellar ataxia and with average intelligence who for obscure reasons were virtually speechless until the age of 5 years. The delayed speech development in these children seems to be comparable to that of most of our patients. It is possible that the three children reported by Ingram were, in fact, suffering from what we call the dysequilibrium syndrome, and that in these cases defective auditory perception might have been the main cause of the ex treme retardation of their speech development. In our experience from cases of congenital cerebellar ataxia, the auditory dysperception in this syndrome is less marked or in some cases non-existent

Another condition to be differentiated is infantile autism. Autistic children usually are self-sufficient and completely indifferent at trials of contact, which is in striking contrast to our extremely mother-dependent patients. However Bender (11) remarked that even children with infantile autism sometimes are very mother-dependent, an observation which makes differential diagnosis between this condition and the behaviour in the child with dysequilibrium more complicated

Sahlmann (75) has stressed the importance of differentiating cases with primary aphasia from the group of infantile autism. In a series of 60 patients with a suggested diagnosis of infantile autism, she found 16 children with primary aphasia. Sahlmann's differentiating signs for distinguishing these 16 patients from infantile autism are in agreement with the findings in our series. Thus, in our children verbal commands were at first ignored, but as soon as some speech ability was achieved, the autistic pattern was broken. At the be ginning of their language development, our patients, like those of Sahlmann, showed a great interest in other people's names. It is interesting to note that the therapy in the aphasic children described by Sahlmann (75) was of the same type as that which has been used for several years at the Folke Bernadotte Home in our children with the dysequilibrium syndrome and also in other patients with aphasia. This consists of physiotherapy ac companied by a steady stream of auditory stimulation, including rhythm on tambourines.

Although serious *hearing defects* are common in patients with cerebral palsy the pure tone audiograms were normal in our series except in two patients with minor defects. Close testing and observations revealed a mix ture of lack of consistent discrimination of auditory stimuli and lack of fixed attention

on a specific stimulus It seems clear that the language defect is due to an aphatic condition. Aphasia, however includes defects of the perceptive interpretative and also expressive functions of the brain. As stressed by Sheridan (78) it is often impossible to decide which of the components is the one mainly affected.

To conclude from the information collected from our series of cases, we believe that the main hearing defects are to be found in the perceptive and interpretative areas, the cardinal factor probably being a defective auditory memory According to Masland & Case (6?) auditory memory includes memory span, memory for sequence patterning of rhythm stress and inflection and finally patterning of phonetic detail. These authors described 4 selected patients with very delayed language development and in these cases they were impressed by the limitation of auditory memory Generally they found a restricted comprehension of language, an infantile level of vocabulary development, impoverishment of phonetic detail of speech and a simplification of syllable, rhythmic and semantic patterns, findings which in all main respects are in accordance with those in our series. As already mentioned, this also holds for the different parts of auditory memory

Thus, even though no complete analysis of auditory perception was made in our patients, due to the lack of suitable tests, it seems probable that the major cause of the language delay and the obvious difficulties in auditory learning in these cases was their markedly defective auditory memory

Perceptual and visuo-motor disorders are seldom seen in patients with athetosis, but very often in spastics. On the whole the severity of a motor handicap as such seems to have a surprisingly low correlation to perceptual disorders, as shown, on the one hand, by patients with serious athetosis but with no perceptual problems and, on the other by clumsy children with "minimal brain dysfunction" but with marked perceptual difficulties.

There are only a few report [illegible] evaluation in children with [illegible] palsy Cases r[illegible]rted have sh[illegible] p[illegible]ceptual and [illegible] to [illegible] 49) but furth[illegible] d[illegible] are [illegible]

Concerning th[illegible] in the 6 of ou[illegible] possible the [illegible] space) and subt[illegible] were especiall[illegible] trend was tra[illegible] related to m[illegible]nta[illegible] H[illegible] sion, based upon o[illegible] the result in the test situation do no[illegible] respond to the pat[illegible]ents real ab[illegible] in daily life To explain [illegible] several factors must be co[illegible]ed.

The firs[illegible] he [illegible] reliability of the value[illegible] btain[illegible] m[illegible]ntal age scoring Probably these values must be considered as absolute minimal levels Most values were obtained from the Terman Merrill test. In a verbal test situation the values must be highly negatively influenced especially by auditory dysperception, a constant feature in the dysequilibric child. Even though the IQ values are considered to represent the actual ability of the children it is not probable that the same factors influence both the verbal IQ test and the Frostig test. For these reasons the scores of the Frostig test may seem falsely high.

A second point is that all the children who underwent the Frostig test (Table 8) had been exposed to visuo-perceptual training of all kinds in their pre-school period. Visuo-perceptual programs built up on the same principles as the Frostig work-sheets evidently had a good effect as it was possible for even the most subnormal patients to learn a certain amount of reading. The children's performances of all tasks of this kind were initially very poor indeed

A third point is that when the sitting position is stable and the child is placed at a table he will to a certain extent compensate for his slight tremor and unsteadiness. When his

working space is limited by two parallel lines, however his eye–hand coordination becomes very poor Sitting is a favourable position, which the children do not seem to want to get away from of their own free will. When sitting his body is evidently a point of reference. His vision is sustained by an intact stereognosis. He is able to learn shapes and their three-dimensional images by manipulation. In our treatment programme feedback to his manipulations and the building up of a shape concept are given to the child by resistance to his movements, which will also hinder him from perseveration. *In standing* and even more so in walking the equilibrium problems are at an extreme. He uses his eyes to seek points of reference for the judgement of distances and for estimation of the movements of objects and people. This means that he has to rely upon his "body sight" Therefore, in standing and walking the dysequilibric child regresses in his perceptual ability to his developmental levels of locomotion and auditory perception, which may mean the 2 and 4-year levels, respectively in for example a 14-year-old child

Thus in children suffering from the dysequilibrium syndrome, it seems as if the Frostig test gives us some even if incomplete, information on the visuo-motor and perceptual functions in the sitting position. The extremely low scores in subtest IV (position in space) are in agreement with the immature body image in these children as demonstrated by other tests (Table 9) Another reason for the very low scoring in this test was in most cases perseverance, cases 1 6 and 9 being exceptions.

However the Frostig test did not give us a true picture of the visuo-motor and perceptual abilities on standing, where the capacity of our patients was far more limited than in the sitting position. This test is certainly of some value but the value is therefore limited, and the results do not give us the total general ability of the child.

The pathogenetic importance of oculomotor disorders in conditions of deranged visual perception has been stressed by different authors, as pointed out by Abercrombie (1) Thus, difficulties in maintaining fixation which was a regular finding in our patients, have been supposed to delay learning to perceive Strabismus, which was found in 6 of our patients, has also been correlated to perceptual and visuo-motor defects (2)

Marianne Frostig (29) points out that body awareness affects not only a person's self image but also his perception of direction She also stresses that a child must learn to perceive an object as being in front of himself before he can learn to perceive objects as being in front of each other A child who has no ability to lateralize and accurately perceive the position and direction of objects becomes frustrated and confused. This seems to be very true for many of our cases. As shown by the low scoring in the imitation of gestures test (Table 9) our patients had an immature self image This, according to the above discussion, may have explained to some extent the slow development of spatial concepts.

It is known that in blind children deprived of hearing, spatial orientation develops slowly Normally from the age of 3 years the proprioceptive inflow the visual element and the spatial orientation are integrated in the development of the mental body image by repeated experiences. However Bergès & Lézine (13) comment that the child under 4 years of age depends more on kinesthetic than on visual elements. In our group the results of the vibration test suggest *a defective proprioceptive integration within the CNS* This assumed defect is probably responsible for the slow development of equilibric reactions and of the dysfunction of the lower extremities. In dysequilibric children it is coupled with poor auditory perception and lack of proper visual integration which seem to be the answer to the question why through the years they keep on bumping into people and furniture Their summarized defects also explain their extremely poor performance in the most simple ball

games, in which they do not seem to know whether the ball is on its way towards them or away from them There are also many other related spatial disabilities handicapping the dysequilibric child. Generally he has a very poor sense of direction length, area, weight and amount. For example, he has great dif ficulty in finding his way about even in buildings that he knows well. This peculiarity was pointed out by Ingram (44) for patients with congenital cerebellar ataxia. A generally poor topographic understanding is a regular finding although these children are able to learn geographic facts by verbal means, it is im possible for them to make use of these facts in daily life The task of paying in a shop can be very difficult, because even if they are able to do arithmetic, amounts of money mean nothing to them.

The psychological implications of a disturbed body image have been discussed by Bender (11). A late developed body image also means a delayed developmental age In our patients the latter was further accentuated by the re tardation of language development. Before the child has developed a body image a pic ture of himself in the world around him and thus an ego he remains a clinging child, ex tremely dependent upon his mother This situation was the rule in our patients for several years and was of course further ac centuated by their extremely poor equilibrium. As stressed by Bender (11) in her study some of the children with a poor body image in order to gain control of themselves and the world around them, developed a stereotypical rigid behaviour This was, as already mentioned, a common feature in most of our pa tients.

To *summarize* in our group the concept of visual perception and visuo-motor ability is characterized by severe disturbances in dif ferent fields. Coupled to these is an extreme delay in the body image development. The auditory perceptional ability seems to be even more deficient and, furthermore, less trainable. Therefore, in educational work, the training in these patients should mainly be concentrated on visual stimulation, this being the most useful of two poor alternatives, although integration of visual and auditory stimulation always should be aimed at. How ever when the patients grow older and a higher educational level is reached (cases 1 and 3), the children, in order to advance, must be trained to utilize all available resources in auditory learning The perceptual situation in dysequilibric children seems to be different from and more severe than in children with pure congenital cerebellar ataxia Although these children are late in their development of auditory as well as visual perception, in time these functions will be fairly good without much training

Oculomotor disturbances are common in patients with cerebral palsy Strabismus and eye muscle palsies were found in 6 of our 13 patients. The importance of strabismus for visual perception has been stressed by several authors. In our patients defective binocular vision seemed to be especially disabling, be cause of the need for good vision in compen sating the dysequilibric state The significance of visual disturbances in the concept of visual perception has already been discussed.

The 3 patients with *cataracts* were not found to differ in any other clinical respect from the rest of the series. It is possible that none of the cataracts were congenital In 2 of the patients their onset was obviously postnatal. Two of the 3 patients were moderately mentally retarded, while one was intellectually normal. No mental or neurological deteriora tion was observed in any of them All three were a little short in stature, their heights being 1–2 standard deviations below the mean values for the age and sex.

The triad cerebellar ataxia, cataracts and physical and mental retardation form a syndrome named after Marinesco and Sjögren (79) This syndrome is considered to be in herited in an autosomally recessive way Ac cording to Alter et al (3 4) it is not known whether the cataracts are congenital or not.

The question whether the condition is stationary or not is controversial. In some of his cases, Sjögren (79) reported a slow but evident neurological deterioration in adulthood while in others the conditions was said to be stationary Andersen (5) described 11 patients with this syndrome, and up to the time of his report he had observed no neurological progression, but in contrast a steady functional improvement. Müller (65) stated that in order to differentiate the syndrome from the progressive forms of heredo-ataxia, the non progressive course of the Marinesco–Sjögren syndrome must be borne in mind Neither metabolic nor chromosome studies have hitherto contributed any information as regards the etiology Usually this syndrome seems to be stationary at least during the first 20–30 years of life From the age of 30–40 years a slow neurological progress cannot be excluded, according to Sjögren (79) Thus the question still remains open of whether the disease in ıe long run is to be ranged within the concept cerebral palsy or not.

With the definition of the Marinesco–Sjögren syndrome accepted at present, 2 of our cases (cases 1 and 4) with mental retardation fulfil the criteria. One further case, a girl born in 1964 not included in this series but with a very characteristic *dysequilibrium syndrome*, also comes under this category

However even if patients with this triad of symptoms can be grouped together as cases of the Marinesco–Sjögren syndrome the main disabilities in our cases 1 and 4 as well as in patients with the syndrome reported in the literature seem to be those of the dysequilibrium syndrome (5 65) It is noteworthy that similar cataracts have previously been reported also in cases of congenital cerebellar ataxia (46) Furthermore, our case 8 has cataracts but is intellectually normal, which does not fit in with the Marinesco–Sjögren syndrome Apart from our familial case 13 we have seen at least two further pairs of mentally retarded siblings with the dysequilibrium syndrome but with no cataracts

Thus there are many different constellation of dysequilibrium state cataracts, mental re tardation and inheritance The common de nominator however is their dysequilibriur syndrome, making the clinical picture in thes otherwise different cases uniform as regard their motor handicap The main importanc of the label of the Marinesco–Sjögren syn drome for the moment seems to be that ı makes a hereditary etiology probable, but i does not alter the therapeutic approach. It i doubtful whether the Marinesco–Sjögren syn drome should be entitled to be kept as a spe cial entity in the future Except for thei cataracts, our 2 patients with the syndrom had the same handicap problems, and bene fited from the same treatment as the others o our series. Furthermore the general outcom in the 3 patients with cataracts at the ages o 8 12 and 21 years, respectively was the sam as in the remaining patients without an changes of the lens.

From the history and neurological, neuro physiological and metabolic findings there i nothing supporting a progressive process in th dysequilibrium syndrome during childhood an adolescence, with reservation for what ha been discussed under the Marinesco–Sjögre syndrome. The clinical picture in our cases i quite unlike those encountered in variou heredodegenerative cerebellar and spinal ataxi syndromes. Thus it is our opinion that th neurological syndrome described should be re garded as stationary with clinical character istics mainly supporting the existence of developmental defects of the central nervous system, but with nothing, except the unsatisfac torily understood cataracts, to indicate progressive neurological deterioration.

E. *Early Differentiation of the Dysequilibrium Syndrome from the Syndrome of Congenital Cerebellar Ataxia*

The clinical picture in the child with the dysequilibrium syndrome in the different stages of motor development has been fully described

in the previous chapters. The cardinal factors which distinguish these cases from the more common and classical forms of so called ataxic cerebral palsy are the dominating signs of dysequilibrium Dysequilibrium, as it has been defined, i.e. incapability of or pronounced difficulty in maintaining posture and equilibrium, is not difficult to recognize in older patients who have left the astasia-abasia stage and have achieved the ability of standing. At this older stage the typical uncompensated falling is obvious and the diagnosis in most cases should be clear The diagnosis is further supported by the presence of the typical "feet up in the air crawling" (not seen in any other syndrome of cerebral palsy) of a primitive language and pronounced defects of auditory and visual perception including a highly undeveloped body image.

There are considerable difficulties in clinical recognition during infancy The dysequilibric child, as in the case of congenital cerebellar ataxia and ataxic diplegia, has the unspecific picture of a "floppy infant" grossly retarded in his general motor development Therefore the differential diagnoses are those encountered in the whole complex of "the floppy infant syndrome"

Ingram (49) certainly is correct in stating "the diagnosis of ataxic cerebral palsy is made on the basis of an increasing index of suspicion This also holds for the dysequilibrium syndrome In the first period of infancy the clinical picture in the dysequilibric child probably cannot be differentiated from that in children with the classical forms of ataxic cerebral palsy so excellently described by Ingram (44 46, 49). Just as in congenital cerebellar ataxia, a positive family history (especially when represented by siblings) should arouse suspicion of the possibility of a dysequilibrium syndrome.

An uneventful pregnancy and perinatal and neonatal period seem to be the rule in cases of the dysequilibrium syndrome Feeding difficulties are, however common from early infancy During the first months it is possible to exclude some other conditions that m[illegible] be expressed as a floppy infant syndrom[illegible] Among these it is necessary to rule [illegible]ut di[illegible]ferent hypotonic states of spinal periph[illegible]ra[illegible] nerve and muscle origin Concerning this p[illegible]r[illegible] of the differential diagnosis reference m[illegible] [illegible]e made to the study of Dubowitz (20)

Kramer & Vojta (55) have recently discussed the differential diagnosis of hypotonia in infancy primarily in connection with the problem of early diagnosis of the congenital cerebellar syndrome" One of their main diagnoses to be differentiated is the atonisch-astatisches Syndrom" a group probably consisting mainly of cases of what we would refer to as the dysequilibrium syndrome These authors state in agreement with Ingram (49) that classical cerebellar a[illegible]ic symptom[illegible] [illegible]annot be recognized before [illegible] age of 6 months i.e not before the motor ability has rea[illegible]hed a certain degree of development However they have attempted to establish criteria on the basis of simple clinical signs with the aim of differentiating hypotonic syndromes already during the first 3 months of life. Their main point of differentiation between congenital cerebellar ataxia and atonisch-astatisches Syndrom" is that in congenital cerebellar ataxia in an infant less than 3 months of age irritability and weak tendon reflexes are found, whereas in the case of the "atonisch-astatisches Syndrom" apathy and lively tendon reflexes are the usual findings.

This formula sounds very neat, but does not fit in with our experiences. We have found that irritability during the first months of life in congenital cerebellar ataxia is very infrequent. On the contrary marked inactivity and contentedness are usually observed, i.e the same finding as in the case of the dysequilibrium syndrome Both in congenital cerebellar ataxia and the dysequilibrium syndrome the tendon reflexes are weak. We cannot, therefore, agree with the differentiation criteria of Kramer & Vojta (55) In our opinion, differential diagnosis between congenital cerebellar ataxia and the dysequilibrium syndrome is

impossible to make in the first months of life Furthermore, from a practical point of view such a differentiation during this early period does not alter the therapeutic approach.

During the following three-quarters of the first year increasing evidence is presented which makes the presence of a syndrome with a disturbed coordination of movements probable. According to Ingram (49), a spastic diplegic component usually can be recognized by the age of 8 or 9 months, an opinion which is in agreement with our experience In some cases, however spasticity may be obscured for many months by anomalous patterns of motor development, e.g. the shuffling pattern, as pointed out by Robson & MacKeith (73)

Predominance of dysequilibrium should be suspected when in infancy there is an unduly slow motor development even compared with most cases of cerebellar ataxia, when there is great poverty of movement associated with complete absence of exploration ability of the wer extremities, when there is scanty vocal with a very poor motorized component when auditory stimulation is not followed oy an adequate motor response Nevertheless, during infancy it is only possible to have a suspicion that "this patient with all probability has an ataxic syndrome, that he has spasticity or not, and that he might have a component of dysequilibrium"

Further evidence is obtained when the motor developmental ability reaches a higher level. A patient with a predominance of dysequilibrium will not be able to sit without support before the age of about 2 years. This fact in itself directly points to the diagnosis of the dysequilibrium syndrome At this stage the fine motor development is much better developed than the gross. The child sits with widely parted legs and kyphosis of the spine. When provoked, a truncal tremor is observed. Babbling is still very scanty and single words will usually not be uttered before the age of 4 years. The behaviour is introverted and stereotypical even in intellectually normal children.

Usually the patient with cerebellar ataxia is more active, babbling or talking, thus giving a more intelligent impression. Truncal tremor is not a distinguishing sign in the dysequilibrium syndrome, because of its presence also in severe cases of cerebellar ataxia. There is, however one sign characteristic of dysequilibrium at the age of 2–3 years. When the child sits on the floor and is pushed backwards in order to make him fall, no balance reactions of the legs are noted the legs instead still remain flaccid in the original position, i.e. usually straight and wide apart. In the same situation it is characteristic for normal children and those with cerebellar ataxia to stretch and lift their legs as a reflex.

If these observations are made at an age of two years the probability that the diagnosis should be a dysequilibrium syndrome is fairly large However there are children who exhibit this behaviour at two years of age, but who during the following year develop rapidly and at 3 years of age show a typical picture of the syndrome of cerebellar ataxia with active behaviour usually talking, walking with dysmetric steps but when tilted showing normal stepping reactions, and exhibiting a distinct intention tremor on active hand movements. At this age (3 years) the truly dysequilibric child has developed only slightly since the age of 2 years, being still unable to crawl, and sitting only inactively

When the dysequilibric child begins to crawl, usually at 3–4 years of age, the style of crawling can be used for differentiating between the syndrome of dysequilibrium and that of congenital cerebellar ataxia The crawling in the dysequilibrium syndrome is very peculiar and may be pathognomonic for this condition. It is characterized by crawling on the hands and knees with extended arms, lifted feet and side to side movements of the head.

Finally the definitive diagnosis can be made when the child is able to bear weight on the legs. The dysequilibrium then manifests itself in an exaggerated supporting reaction with rigid pillar like legs, the absence of compensat

Table 11 *Some differential characteristics of the syndrome of congenital cerebellar ataxia and the dysequilibrium syndrome*

	Cerebellar ataxia	Dysequilibrium syndrome
Truncal tremor	Non-dominant	Regular in stages I–III
Parachute reactions	Normal	Late developed and backwards, abnormally slow
Supporting reactions	Normal	Exaggerated in stages II–III
Stepping reactions	Almost normal rate	Absent or very slow
Crawling	Normal style	Typical "feet up in the air" style
Walking achieved	2 5 years	6–9 years
Falling	Incoordinated but "normal" on the knees	Usually backwards, clown-like and full length
Running	Usually achieved	Probably never achieved
Hand skill	Can become almost normal	Arrest t 4-year level
Motor and mental activities	Except for the first year rather active	Typically inactive and negativistic
Language (partly IQ-dependent)	Single words started t latest 2 years of age, typical scanning	More delayed, primitive sentences. No scanning
Auditory perception	Usually no dysfunction	Extremely poor Limited auditory memory
Visual perception	Probably some dysfunction	Marked dysfunction in different function areas
Body image	Subnormal	Extremely delayed

ing movements of the feet and the body when tilted, and the rigid and uncompensated falling backwards and sidewards like a felled pine

Up to the present, we have found no neurophysiological or other laboratory aids which in addition to the clinical observations might help in the differential diagnosis between the syndrome of congenital cerebellar ataxia and that of dysequilibrium. From a didactic point of view we have compared, in Table 11 certain distinguishing clinical characteristics in each group At the same time, it must be stressed that the differentiating points mentioned above are mainly valid for extremes of the two syndromes under consideration. It is quite clear that transitional forms exist—with a mixture of both syndromes—giving a continuous spectrum from cases with almost pure cerebellar ataxia or cerebellar ataxic diplegia, on the one hand, to cases with almost pure dysequilibrium or dysequilibrium with diplegic spasticity on the other In fact, these mixed cases might be more common than we believe today However the most important thing is to be able to distinguish cases with predominance of dysequilibrium from the large group with congenital ataxia—ataxic diplegia, because of their special problems, the need of intensified therapy and their specific prognosis.

CHAPTER VII

OBSERVATIONS ON THE DYSEQUILIBRIC CHILD IN RELATION TO THERAPEUTIC ASPECTS

The aims in therapy and education must of necessity be modest for most cerebral palsied children, but this is especially so for the group under discussion. The main goal at all stages of his development should be, in our opinion, to help the child with the integration of his sensory inflow to adequate environmental responses.

There are several problems that impede the attainment of this goal, some of which are environmental and some lying within the child himself In normal development the activities of the child influence his social environment, which produces responses which, in turn, modify his social actions. Not many such inter actions take place spontaneously and unconsciously if for some reason the child is very inactive and silent.

It seems as if the social environmental re sponses to the long standing unsteadiness of our patients and their consequent total de pendence are over-anxiety over protection and excessive support which will stand in the way of the child s development to his full potential capacity

Early treatment and full knowledge and understanding of the behaviour of the child usually gradually change these attitudes and create an active environment that will produce active responses in the child and in turn reward from the human surroundings. The child is, however really dependent physically on his mother and his environment, as his first and last problem is that of equilibrium and muscle tone.

The pursuit of equilibrium in a child who is no longer a baby in the common sense, as the stage of floppy inactivity" may last for as long as four years, can create uncontrollable anxiety withdrawal and stereotyped behaviour Only 2 out of our 13 patients did not react with frustration These 2 were later assessed as having a low mental capacity and pseudo-athetoid movements (cases 2 and 12)

Frustrated children rarely establish inter personal relationships other than with their mothers. The mothers must be taught how to stimulate compensatory pathways so that the child will eventually acquire better equilibrial reactions and hence more independence.

Other difficulties will arise from other components of the cerebral dysfunction, which will have to be handled with the utmost patience, understanding and imagination. In short, he is a non-starter a non-stayer a non-converter as well as a non verbal child. Impaired motor activity language disturbances, and perceptual motor handicaps, regardless of severity always tend to manifest themselves in behavioral de viations. Enhancement of the development of the sensory motor function, language, per ception and higher thought processes will usually lead to a better level of emotional and social adjustment.

A. *The Stage of Floppy Inactivity*

General considerations

For children with a syndrome of dysequilibrium, the primary goal and the fundament of all treatment planning must inevitably be good posture and as stable equilibrium as possible Distractibility withdrawal and delayed response are symptoms which in this group of children are closely connected with their dysequilibrium syndrome.

According to the results of the motor test performed in our study (Table 5) children with the dysequilibrium syndrome will not achieve better basic balance patterns than those of a 21-month-old normal child. Equilibrium in healthy adolescents, on the other hand, is no

stable steady state but a dynamic process for the balancing of forces acting on the body from all directions.

Normal children under the age of 24 months have problems with their balance since they have not yet learnt to integrate the visual input, proprioceptive sensations from tendons and joints and information from the semicircular canals of the inner ear to an image of their body in space During growth and from experience, normal children become automatically aware of the body schema. Equilibrial reactions vary between visible adjustments to fine oscillation. The body weight is automatically shifted so that the centre of gravity is more or less always directly over the supporting base. The body leans towards the opposite side to that on which a load is carried. All this has to be taught to the child with dysequilibrium, since by experience alone he will learn extremely slowly

Dysequilibrium occurs when a person cannot balance gravitational forces smoothly and evenly Adjustments and counteradjustments become visible actions. In the young child, dysequilibrium may first be noticed as a coarse truncal tremor and delay in unsupported sitting until an average age of 24 months (Fig. 4). Developmental examination very often reveals that the child is unable to lift his head in the supine position. His head lag is comparable to that of the normal 3–4 months old child. In this respect he is at the same developmental level in his legs, i.e. the astasia stage. His tilting reactions are usually at the 5 months level.

Training

A considerable part of the training must be concentrated on getting the child into a mood of tolerance to handling and abdominal muscle training in the supine position combined with head-lifting and tilting. Simple aids like home-made "splints (thin pieces of wood of the same lengths as the legs of the child put into folds made in a piece of material that can be wrapped around the child's leg and tied at



Fig 1 Two-and-a-half-year-old boy with all signs of the dysequilibrium syndrome, demonstrating the use of home made "splints" A normal girl of the same age is seen to the right.

at least three different points) is necessary both for certain sitting training and for use with a standing table or on the tilting table (Fig. 17). Because of their poor muscle tone the legs are too flaccid to serve as stabilizers in sitting. Heavy sandbags placed over the legs will therefore improve the sitting balance considerably In our experience, keeping the legs cool and approximation of all the joints involved in standing or the cautious use of a small tilting table will in different ways "switch on the gamma system" Diagonal pressing and pushing movements on the shoulders whilst the child is sitting on a thick sponge mattress will facilitate the development of a more S-shaped spinal curvation from the C-shaped curve seen in the infant. Stimulation of gross arm movements in play with water sand and fingerpaints, for example, has very often to be facilitated in diagonal patterns (PNF*) as the

* Proprioceptive Neuromuscular Facilitation.

child has no body image also as far as his arms are concerned. To enable him to recognize what he is doing the child may be started with play material in the vertical plane

The visual field perception may not be sufficiently broad and steady for all visual cues to be perceived but should be encouraged in all positions and be reinforced by visual and auditory stimulation To evoke speech function more attention must be directed upon auditory stimuli This form of therapy seems to produce the babble and speech responses desired.

B The Crawling Stage

General considerations

The ability of adequate coordination between the hand and the eye is markedly delayed Therefore in upright positions manipulations tend to be more tactile than visuotactile Resisted movements are in our experience the only way to make the children visually aware of what they are doing As the mind and the eyes seem to be occupied with optical righting reactions the postural reactions of the eyes are not automatically inhibited when equilibrium is attained. This has to be kept in mind when training the child The incitation to play must be initially very strong to make him focus his attention upon things that normally will make a child forget everything" without any special stimulation

The therapeutic approach must of necessity be a patient one as the child seems to have an obsessive need to maintain sameness. He will show preference for play material of commensurate characteristics, such as toy cars and bricks, and place them in neat rows. One has to hide certain materials in order to break his behavioral pattern He does not show any urge to find them All children in the group under study showed some degree of perseveration with their play material as well as with their speech, and exhibited ritual movements. This was very often mistaken by the staff and parents for great activity and normal play Puzzles seemed to be the kind of material that appealed to these children, and they were often quite clever with them as long as the puzzle did not require analysis but could be made up by the trial and error approach. The children were also very often able to identify and name shapes but had great difficulty in reproducing them on paper (Fig 18).

The teaching of the building up and interpretation of shapes and patterns should be preceded however by body image training Another aspect in the training of such a child apears to depend on our ability to supply and present the perceptual-motor skills which he seems to have difficulty in developing for himself We prefer to do this in natural situations of play and in games (30)

Body image training

Body image training is meant to highlight muscle, joint and vestibular sensations. Probably because of his distorted sense of equilibrium and delayed general development, this child is not a centre of the world around him, as is a normal child His own body is not the accurate reference point for the interpretation of things outside When he is small and is sitting in a cradle being gently rocked, he may fall over but will make no attempt to raise himself to the sitting position again if the muscles are not stimulated. When he is crawling around in his very peculiar pony style, he is like a mechanical toy animal in the sense that he will stop and sit down if something is suddenly put in his way instead of climbing up on to the obstacle or avoiding it by crawling around it. He may sit or later in life, stand "frozen" in this way for a long time until somebody helps him to get started again.

It is essential to break up the behaviour patterns outlined above, which are typical for all our stages" and which are also reflected in the child's speech. To make his own body as much a point of reference as possible seems to be the only way in the long run to help the

child to cope with the problem of appreciation of body position in its generalized sense

Simple movements such as rolling, creeping and crawling can be performed to music or to the beating of a tambourine in order to improve the child's attention span and understanding of spatial relations. Gesell & Armatruda (32) have described tactility as the oldest and most fundamental of the senses and hearing as a specialized form of touch which makes the organism aware of vibrations of distant origin. They state "Like vision it is a distance sense which enables the individual to get in touch with what is spatially remote" Music restricts space in many respects Its use in therapy will lead to more rapid reactions and better orientation in space It is a good way to introduce the child to group activities.

He should be encouraged by members of his family to beat the tambourine himself and to take the lead in performing the movements. In this way he will perceive himself visually and emotionally as the centre of a constricted world of which he is the master

In older children we have used ballet music, getting the children to lie still on the floor and imagine various movements, when they have completed their own performance.

Balloons and soap bubbles have good qualities for body image training. Innumerable games of the give and take speak–do look, feel and see character should be invented, modified and rendered increasingly difficult Gaining control over the limbs in the pool by taking advantage of the water turbulence or chasing floating objects will give the child some automatic control mechanisms if pool exercises are repeated frequently enough.

C. *The Standing Stage*

General considerations

At this stage, our patients try to compensate their dysequilibrium by increasing their base of support by means of a broad-based standing posture and by lowering their centre of gravity by slight bending of the knees. The movement of the thigh is not always successfully transferred to the knee and foot joints, which may result in genu recurvatum and hence instability (Fig. 19). The toes seem to fight an uneven battle to help in the attempts at finding equilibrium, moving up and down in a typical way

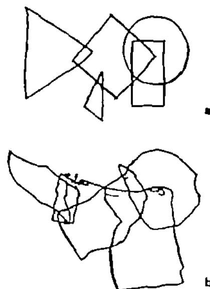


Fig 18 Showing the poor ability of case 6 for reproducing shapes at 8 years of age. (*a*) Test drawing. (*b*) Patient' reproduction.

Anxiety very often causes negative reactions to balance training and a negative attitude on the whole. The child evidently realizes some of his strengths and weaknesses and will not easily conform to other more expected modes of conduct. One thing that is striking, however is that he never cries when he suddenly collapses and bumps on the ground and hurts himself He is a complete fiasco in many other situations and as failures are so frequent he may very often cry for such reasons, however

Achievement of an adequate positive supporting reflex is a dominant feature of this stage. All positive supporting reflexes result in an increase of the extensor or flexor tone to give the body resistance to the forces of gravitational pulls.

Pillar-like stiff legs are a problem in many situations when reciprocal positive supporting



Fig 19 Case 5 at 9 years of age. Standing with broad-based support and marked genu recurvatum.

reactions are needed Learning to ride a tricycle may take an unduly long time but after 6 months or a year it is usually an acquired skill that is very helpful both in managing of the child and in therapeutic situations. He will learn to estimate his and other peoples' speed and distances even if at times this seems im possible The pedalling of the tricycle should be made heavier in the beginning by friction arrangements, and gradually this load should be lessened.

Speech therapy

Riding on a tricycle will also make the speech more fluent, as breathing always improves when the body is in rhythmic motion In speech therapy advantage should be taken of the child's interests and tricycle maze games are especially helpful. These games can easily be reinforced and the child can be helped to generalize his experiences while playing with a doll's house or by making a drawing of the maze Terms such as in front of" behind at the back" round the corner" can be discussed The making up of crazy sentences appeals to the often bizarre sense of humour of these children

Preschool activities

Preschool activities should be carried out as far as possible in the standing position. Visuo-perceptual tasks should also be performed in the vertical plane, as this is something that the child will not develop on his own because of unsustained postural reactions of the arm and shoulder girdle In some cases the per formance is very poor a tilting table might help the child to find his stabilizers in other parts of the body Group activities should stress the interpretation of movement, as this is vague and poorly defined. The teacher should make the child notice sloping lines in everything around him and teach him experimental play with empty boxes and cartons, etc to be found in the home The teacher will have to persuade the child to use the slide, and to help him to jump and climb during free play It may help to use choral verbal tags like "we are going up up up, we are jumping down" The child should always be given the verbal association as a complete sentence, as his own language is very rudimentary Domest ic play activities contain most of the kind of training he needs

Formal education

In our series, in 2 cases (nos. 3 and 5) where the general intellectual level was about 4½ years and they had not yet started to talk, we tried to teach reading by the look and see method to enhance speech. The results were most encouraging. In these cases the auditory perceptual disturbance was reminiscent of autism (case 3) and deafness (case 5) The children acquired a strange affection for their own words and showed great pride in reading them out. Sound analysis developed spontaneously (case 5). Sentences made up of three

ker words were no more difficult to re ... than long words.

D *The Walking Stage*

...ral considerations

...is stage the muscular dyssynergia is more ... than in the earlier stages and is com... with the dysequilibrium. As a result ... are jerky and poorly controlled move...

...e dyssynergia is visible in most hand ...ments requiring fine motor coordination. ...not accompanied by uncontrolled move... in the face On the contrary the face ...ask-like The patient has no difficulty in ...ng on to a pencil, coin or pellet for ...ple, but he gets intention tremor ... phase of grasping an object and ...nal act of placing it in or on top of ... of equal or smaller dimensions ...he is going to lift an object th... ob...ly heavy to everybody else one ... truck ...is lack of automatic estimati... of the ...ular tone needed. He cannot ...ute the ...ng action without producing ... imal voli...al effort and having 3–5 t... s at it If ...e is nobody there to enco... ge him he ...s up after one or two trial...

...n the same way as there ... dysmetria of ...d movements, there is als... dysmetria of ...ps. He usually learns to w...lk upstairs to ...gin with he does this sideways, dragging ...self up with the help of the hand-rail. ...cending stairs is far more awkward and ...kes a much longer time to learn The speech ...slow and in younger children very agram...atical. There is improvement in speech when ...e children have learnt to read The phona...on is very much like that of deaf children

Physiotherapy

...egative supporting reflexes must be evoked ...by training. Flexion of the leg should be fol...lowed by "placing" and extension as promptly ...as possible. The tambourine can be a great ...help to make the child see the difference be...tween and effect of long and short steps. In addition his reactions become trained A tilting-board which tilts in all directions is another type of material that can be used to advantage.

As motor impersistence is a characteristic feature, the value of keeping the body or a limb in a certain sustained position must be emphasized in physiotherapy Lifting heavy objects, especially when kneeling is very effective but the movements have to be facilitated passively in order to initiate the child's own actions. Sustained contraction—i.e slowly putting down heavy objects or just sitting down without collapsing—is also an essential part of the social training

Practising for speed and accuracy

Rasch & Burke (70) have pointed out that speed of movement should not be confused with haste in performance In most gross skills speed implies the application of great initial force. In a learning situation, resistance applied against the child's movements is necessary the encouragement to the performer might well be "harder" or "come on" rather than "faster" Under pathological circumstances, general haste is likely to cause activation of a large number of muscles through radiation of impulses.

Achievement of a skill very often requires both high speed and great accuracy Children such as those in our group are unlikely to acquire many such skills. However it should be emphasized that speed and accuracy should not be taught separately

Improvement of walking

These children lack flexibility in all types of motor performances. They cannot readily adapt to changes in environmental conditions Physiotherapy should provide a wide ... mental variety including such ... as skiing and skating.

In the case of this group of children walking must be looked upon as a ... skill. He must concern himself with where and how

he shall put down one foot in front of the other In the learning situation resistance should be applied to the leg that is being lifted so that the child will tilt the body to the opposite side and take all the body weight on that leg. The children prefer perambulators and rollators but we have persisted in getting them to learn to walk with sticks or saw-crutches to establish automatic tilting reactions It may take a year of daily training to teach one of these children to walk indoors independently and another year to teach him outdoor walking In outdoor walking the topographical conditions are as great a problem as his poor topographic vision

The saw-crutches and sticks are often carried in front of the body when the children feel more safe The crutches or sticks are hence used in the same manner as the acrobat uses the limber pole to lower his centre of gravity

When the children grow taller and heavier and better proportioned, and muscular tone is more controlled compensation mechanisms (vision and hearing) make walking comparatively fast and steady However motor controlling cerebral mechanisms will probably always work too slowly to allow running Broad-based jumping without falling seems to be the limit of controlled gross locomotion.

The gait will always be characteristic with the feet in outward rotation in the younger child slapped on to the ground with the ball of the foot first In the somewhat older child the feet are lifted high and put down in a slow tentative manner but with a narrower base of support compared with the younger child He gazes steadily upon the ground In the child who has only just learnt to walk, the arms are raised in front of him, the chin is held higher than normally and he keeps staring straight in front f him When told to carry a glass of water and to look at the water he will start zigzagging Arm swaying during walking occurs very late in life in these children. If it does develop arm swaying will abolish exaggerated rotary head and trunk movements—which are [illegible] exaggerated also in healthy subjects [illegible] swaying is absent (17)

E. *Problems in [illegible]*

Eye movements

Most of the children [illegible] their heads tilted to one side as if [illegible] binocular vision They have great [illegible] in keeping their gaze fixed upon [illegible] their sight seems to get blurred after a [illegible] period of sustained fixation, the [illegible] look up at intervals. To make their [illegible], a type of eye hand coordination [illegible] intervals has been successful

Motor impersistence

This is a developmental [illegible] which can be measured by standard [illegible] (87). These authors found it to be [illegible] with dyspraxia (the inability to [illegible] purposive movements in the absence [illegible] or paralysis) Normal children [illegible] old were used as controls. The ch[illegible] series could not keep their tong[illegible] 20 sec nor their eyes shut Th[illegible] take a deep breath and say "ah[illegible] than 5 sec, nor keep their gaze [illegible] visual field for 20 sec even whe[illegible] 19 or 20 years old (cases 1 and 2) [illegible] six 9–10-year-olds were able to per[illegible] of the above tasks (cases 4 5 6 [illegible] and neither could case 3 who was 13 [illegible] We noticed, however that games [illegible] in which persistence in different [illegible] required, was a very good way to [illegible] children with this defect

Hand position

In her monograph concerning hand [illegible] in 224 preschool children the Swedish [illegible]logist Carin Uhlin (82) pointed out [illegible] hand position automatically changed [illegible] pronated to a more supinated positi[illegible] the child no longer used the distal arm [illegible] as prime movers She made a spe[illegible]

of 40 children with regard to hand position during cutting exercises. In the age group varying between 5 and 5 11/12 years the children kept their elbows steadily abducted when manipulating scissors and paper They worked with their hands in semisupination. At the age between 4 and 4 11/12 years the elbows were not held in a steady abducted position and the hands were only one quarter supinated. At the age between 3 and 3 11/12 years they kept their elbows abducted but the hands were in full pronation. In our group of children the development towards a supinated hand position was pathological, not because of spasticity which in cerebral palsied children is a common cause, but because of adduction of the upper arm or pressing of the forearm against the thigh or the table in order to improve their incoordinated voluntary movements. This, in our opinion, will impair learning of skilled movements and speed. Exercises with skittles seem to be more effective than more complicated arrangements.

F *Formal Education*

Difficulties in reading and writing are bound to occur as a direct consequence of the nature of the handicap In patients with the most severe difficulties of this kind in our series resort to an auditory system of learning and the fostering of such potentials as memory and associations made it possible for some of the patients to make further progress in their schoolwork (cases 1 2, 3, 4 and 10) Mechanical learning was frequent in all subjects. The time and number concept formation was very impaired and was hence a great social problem for the child.

Phonation and the rhythm of words and sentences should be trained with the help of a tape-recorder and a tambourine Items such as how much?" how long?" heavy or light?" should be introduced into games. Dramatic play is to be recommended as it gives speech and social training, as well as training in spatial concepts.

G *Effects of Therapy and Education*

Only close cooperation and an overlapping integrated approach on the part of the therapists and teachers will give any lasting results or concepts. The following improvements were noted in our series. As we had no untreated control series, it was impossible to decide which of the improvements were spontaneous and which were due to therapy

1 Therapy and knowledge, e.g. help to and understanding of the child and the mother changed the atmosphere around the child in a positive direction. The above outlined approach seemed to break up autistic tendencies or withdrawal patterns so common in these children, particularly during their first 4 years. Their behaviour seemed to conform to more normal patterns as selfconcept was acquired. Finally interaction with other participants in the community became possible

2. Gradually more stable equilibrial reactions and development of eye–hand coordination, coupled with an ability to imitate other peoples actions and movements were noted.

3 There was better persistence of movements and muscle synergia followed by a longer attention span.

4 Activation led to higher auditory attention and thus improved their speech and concept formation. The obsessive need to maintain sameness was replaced by pedantic rituals.

5 There was improvement of the body concept, hand function and equilibrium help with the adaptation of the sensory inflow seemed to have given the inborn potentials a fair chance of development towards an appropriate form of formal education.

6 Better physical and mental concepts seemed to be acquired even in late adolescence when therapy and education were continued (cases 1 and 2)

From an occupational point of view a sheltered workshop or an otherwise designed job does not seem entirely impossible when the children are about twenty but might depend upon when therapy and education are started.

CHAPTER VIII

GENERAL DISCUSSION

Cerebral palsy is a concept not referring to any special disease or lesion but created today mainly from the need of society for specialized management, including physiotherapy educa tion and general care of a defined but very heterogeneous group of patients with cerebral dysfunction resulting in a stationary motor handicap syndrome Within this concept a variety of clinically pathologically and etiologically different syndromes are found. For some of them, for example athetosis after severe icteric states, the perinatal cause and its nature are obvious and the pathogenetic mechanism is quite clear Other syndromes, particularly those of ataxia, are clinically less well defined and the etiology is essentially unknown. In most cases of congenital ataxia, prenatal developmental factors are considered to have been at work.

The negative peri- and postnatal histories in the majority of our patients with the dysequilibrium syndrome described here speak in favour of a prenatal origin in these cases also There is, however probably no single common causative factor in this syndrome, and a heterogeneous etiology seems more likely Some cases may be genetically deter mined, others may be due to non-genetical errors of brain development, and in others again there may be a brain lesion acquired during intra-uterine life

Ataxia is a descriptive term implying signs of dyssynergia and appearing in disorders with various pathogenetical backgrounds. The term is widely and vaguely used in the literature, unfortunately without any strict criteria for definition. This seems to be particularly valid for its use in publications in the field of pediatric neurology

Cerebellar damage or maldevelopment is known to produce the usual type of *ataxia* with mainly motoric components, clinically characterized by incoordination of voluntary movements causing signs such as dysmetria, intention tremor and an unsteady dysmetric gait.

So called *sensory ataxia* (69) is the other main type This is usually associated with defective afferent inflow to the important supraspinal centres regulating motor activities. In its classical form tabes dorsalis is one example with interruption of proprioception at the cord level. Severe neuropathy may cause similar ataxia with a more distal block of afferent impulses. Patients with "sensory ataxia" have an unsynchronized gait, because they do not know how they place their feet, owing to lacking kinesthetic information from the muscles and joints. The pathophysiological mechanism in these cases is rather different from that in cerebellar ataxia.

Thus, ataxia in the broad sense includes not only dyssynergic muscle movements but also an unsynchronized gait due to defective proprioceptive function on different levels. This difference between cerebellar and sensory (spinal) ataxia is pointed out by Mettler & Orioli (63) who also make a rule for differ entiating between them, claiming that the gait in spinal ataxia is loose, irregular and disorderly in contrast to the alternating, shaking character of cerebellar ataxia. Other authors (23), however have found the possibility of clinical differentiation between these two conditions very difficult or indeed impossible.

The gait in our patients with the *dysequilibrium syndrome* is more like the gait in spinal ataxia as described by Mettler & Orioli (63), than that in cerebellar ataxia. Another similarity to spinal ataxia is that in dysequilibric children the function of the upper extremities is much better than that of the lower However even though there is marked dissociation of the motor function, all body parts are

affected in our cases, and clinical and neurophysiological examinations indicate that the dysfunction is not of peripheral origin

Mettler & Orioli (63) also stressed that it is necessary to differentiate between the two ataxic conditions mentioned and dysequilibrium, even though dysequilibrium and cere bellar ataxia often occur together" We certainly agree with this statement. The same authors describe dysequilibrium as a condi tion characterized by affection of the bodily musculature as a whole They state Disturbance at rest is evidenced by the assumption of tense postures and a strong disinclination to move Wide, deviated, and lunging forms of locomotion with rolling, swaying and twist ing all may be seen in dysequilibrium" This description fits in all essence with the clinical picture in our patients, although the signs in the dysequilibric child are dependent on the stage of motor development.

According to Mettler & Orioli (63) dysequilibrium may arise from injury to the vestibular system proper and also by interference with the floccular nodular lobe and its associated deep nuclei and connections. This concept is in accordance with the opinions of Marshall (60) and his description of the floccular nodular lobe syndrome" In our patients the results of vestibular tests were normal, leaving a dysfunction of the floccular nodular lobe as a more plausible pathogenetic factor However from reasons given below the problem is not as simple as that. It seems to be possible, for example for almost identical clinical pictures to be produced by very different types of lesions or maldevelopments of the central nervous system It is not inconceivable that the common denominator consists of an *inability—located at different levels in different cases—to integrate a normal proprioceptive inflow* In our patients, the weak falling reactions in the vibratron test (as described earlier in the paper) support this hypothesis. It is probable that a deficient response to afferent proprioceptive impulses may cause the dysequilibric child to fall full length without any compensatory movements The body image functions on a subcortical level seem to be congenitally defective Secondarily this results in an impaired development of the body image and of the spatial relationships on the cortical conscious level.

Compared with patients with dominant cere bellar ataxia our patients with the dysequilibrium syndrome showed a much more complex pattern of symptoms and signs. This included a predominant component of postural dysfunc tion and hence dysequilibrium, and, in addition, a minor component of dyssynergia with dysmetria and slight intention tremor perceptional disturbances of hearing and visuo-spatial conceptions, including body image, and a typic ally disturbed speech Most of the patients were mentally deficient.

In the following, aspects of different mor phological changes as well as possible levels of dysfunction in this multifacetted syndrome will be discussed mainly in the light of pre vious literature. Furthermore, the place of the syndrome within the classification schema of cerebral palsy will be considered, particular ly its relation to the concept of ataxic cerebral palsy" Finally some concluding clinical re marks concerning early diagnosis and manage ment of these children will be made

A. *Morphological Aspects*

The literature describing autopsy findings in patients who might be considered to have had this syndrome is meagre Foerster's (24) cases of atonic-astatic cerebral palsy" accompanied by "spastic symptoms showed "frontal scler osis their cerebellum being structurally normally developed. However the cerebellum was not examined microscopically No information was given concerning the globus pallidus.

Anton (6) described a child with a congenital disorder whose *main trouble* was one of inability to maintain equilibrium Autopsy revealed aplasia of the cerebellum, high hypoplasia of the striatal bodies, Deiter's nuclei and an absence of ...

bellar pathways The globus pallidus was nor mal.

At autopsy of a mentally deficient child with "atonic diplegia" and apparent loss of equilibrium Druckman et al. (21) found lissencephaly with anomalous formation of the cerebral cortex, thalamus and medulla and a generally small cerebellum In addition, loss of Purkinje cells and gliosis were interpreted as secondary to anoxia caused by multiple seizures. The authors also referred to a personal communication from Yannet, who found in one patient a loss of Purkinje and granule cells in the cerebellum and in two siblings a loss of cells in the pallidum

Congenital primary atrophy of the cerebellar granular layer (67) a pathological entity described by several authors in some cases, seems to be manifested clinically by a dominating disturbance of equilibrium (35 50 51)

In one neuropathologically examined sibling of three with identical clinical pictures, hypoplasia of parts of the cerebellar vermis (especially the posterior portion) correlated clinically with marked dysequilibrium and very pronounced hypotonia (37) Almost identical clinical and pathological findings were reported by Juobert et al. (52) who had the opportunity of making a neuropathological examination in one of four siblings with the same clinical picture Contrasting with these reports is a review by de Morsier (64) of patients with agenesis of the cerebellar vermis, where he states that such a defect is not manifested in a cerebellar syndrome in man

Marshall (60) described the "floccular nodular lobe complex" a clinico-pathological entity on the basis of studies of cerebellar ablations in animals and findings in patients with cerebellar tumours The clinical picture produced in the animals and observed in the patients was one of severe disturbance of posture and equilibrium. In a study of patients with tumours of the posterior vermis, Brown (16), found nystagmus in all directions in most cases, a sign which was not present in our patients.

In their extensive pathologico-clinical study of cerebellar damage in alcoholics, Victor et al. (83) found no support for the hypothesis that the floccular-nodular lobe is essential for the maintenance of equilibrium. Their diverging opinion was based on a study of patients with involvement of this part of the cerebellum.

The sister of our case 13 with an almost identical neurological picture, died at the age of 5 years. When she was 1 year old she developed serious vaccinia gangrenosa (43) The cause of death was disseminated chicken pox. At autopsy (12) an irregular cytoarchitectural pattern of the temporal, frontal and occipital lobes was found In both the vermis and the hemispheres of the cerebellum there was dysplasia of the Purkinje cell layer In the caudate nucleus and the putamen the same "immature" appearance of nerve cells as found in the neocortex was observed, whereas the pallidum and thalamus appeared normal. In the lateral pyramidal tracts there was an obvious loss of myelin sheaths which was interpreted as being possibly due to retarded myelination. Degenerative changes were found not only in the spinal ganglia and dorsal nerve roots but also in the myelin sheaths and the axons The authors found these latter changes difficult to interpret, but considered that they may have been due to toxic effects of the vaccinia gangrenosa and probably had no connection with the dysplastic changes of developmental origin.

Recently our case 13 died of an infection. The preliminary results of the autopsy[1] now available showed very complex and widespread brain changes due to secondary septic, necrotic and encephalitic processes. No major developmental abnormalities were found. However the cerebellar cortex and the size of the cerebellar foliae were reduced. At a preliminary examination no significant microscopic changes consistent with cellular dysplasia were revealed in the cerebellum.

Thus the documented neuropathological

[1] The xamination was kindly performed by Professor P Sourander Gothenburg.

findings diverge markedly indicating that differently located defects can give identical, or at least very similar clinical pictures. In addition, different clinical expressions are to be expected from a pre or perinatally acquired cerebellar lesion than from a similarly located lesion acquired at an adult age It is of interest in this connection that Stewart (80) in his review of patients with cerebellar agenesis, remarks that almost complete agenesis of the cerebellum is known to be compatible with a normal life

B *Aspects on Possible Level of Equilibrial Dysfunction*

To maintain a steady equilibrium, man is dependent upon afferent impulses from the eyes, the vestibular organs and the somatic proprioceptors. Equilibrium on a firm base is almost exclusively dependent upon somatic proprioceptive influences, according to Martin (61) The patients of our study were characterized by extreme difficulty in maintaining an upright posture even on flat ground, and a marked dependency on visual compensation In spite of visual perceptional defects, their ability to correct their position from visual impulses seemed to be normal, speaking in favour of a functioning tectocerebellar pathway Their vestibular function was found to be roughly normal, as proved by rotational tests.

Thus, dysfunction due to visual or vestibular defects seems to be excluded as an explanation in these cases. With all probability the failure is to be sought somewhere along the proprioceptive pathways on their course up to postural reflex response points.

*The afferent proprioceptive pathway in*cludes peripheral nerves, spinal pathways, the thalamus, the parietal lobe and the cerebellum. Martin (61) considers, from his study of patients with postencephalitic Parkinsonism, that the afferent pathway ends in the globus pallidus, which he considers to be the centre for postural reflexes and hence equilibrium.

In our cases, the findings at neurological examination and the normal results of neurophysiological tests, including nerve conduction velocity studies, excluded defects of the *peripheral nerves* as a cause of the proprioceptive dysfunction

The clinical picture is much the same as in cases of *spinal cord* dysfunction with posterior column ataxia" In agreement with this observation the gait of one of our older patients (case 2) 10 years of age was said to resemble closely that of a tabetic. It is also interesting to note that years before some of our patients were able to walk, or even stand, we found that they could walk better on their hands than on their feet, if the feet were held. However we found nothing else to support spinal lesions. The tendon reflexes were weak in most cases during the first years, but later became normal. The superficial, deep somatic and vibration senses were found to be normal in those patients who could be evaluated Furthermore, the feet were not the typical equinus feet seen in Friedreich's ataxia, but on the contrary showed a pronounced valgus deformity

The *thalamus* is considered to be an important relay station for afferent impulses on their way to final cortical integration, including proprioceptive afferents as well as auditory fibres. It probably also has a selective function In our patients, this thalamic relay station would seem to have been functioning, at least to some degree, as proved by the normal results of the sensory tests. Whether in our cases, the auditory dysperception and other more subtle discriminative sensory dysfunctions might have been due to an impaired selective function of the thalamus is impossible to decide

The *parietal lobe* is responsible for the integration of sensory stimuli, including kinesthetic information. By a steady flow of information a picture of the body image and spatial relationships is built up Our patients were found to have roughly normal proprioceptive senses, although the muscle vibration tests suggested a minor disability In contrast, the develop-

ment of the body image and spatial relationships in these children was severely retarded. However there is no passive reception of information into the parietal lobe but, because of a feed-back system, rather an active gathering in (84) A defect of the feed-back system would explain many of the signs in our patients, as being due to defective or distorted information leading to the parietal lobe This applies particularly to the defective body image and spatial ability in spite of a roughly normal function of the somatic proprioceptive senses. Such a defect might also be the cause of the initial hypotonia.

In the above mentioned feed-back system, the *cerebellum* is considered to be of cardinal importance. Although the main handicap in our patients was their incapacity for or marked difficulty in maintaining posture, they also had *dyssynergia* of their muscles with *dysmetria* of the extremities and, at least to a minor degree intention tremor i.e classical signs of cerebellar dysfunction Concerning the sign "dysequilibrium" the encephalographic findings in the patients of this series, as well as in some others, presented earlier suggest that a defective cerebellar vermis may be of major importance This defect can be manifested as macroscopic hypoplasia or atrophy or only as abnormalities on the cellular level.

Some patients with postencephalitic Parkinsonism and defective function of their *basal ganglia* described by Martin (61) had much in common with our patients, especially the disturbed equilibrium, including falling with no compensatory reactions However our patients had none of the "positive" basal ganglia signs seen in Parkinson's disease patients, such as pronounced spontaneous tremor and cog wheel rigidity

Monkeys poisoned with carbon disulphide showed very selective brain damage, in the globus pallidus and substantia nigra (71) The main clinical result was postural dysfunction and dysequilibrium. But these animals also showed a severe spontaneous tremor and cog wheel rigidity

It is obvious from the above discussion that the central mechanisms and the central connections for the equilibrium servo regulation make up a very complex and well integrated system, where we have to consider the cerebellum, thalamus, pallidum and parietal lobe, and perhaps also other structures. To decide, from clinical tests in individual patients, which central structure or structures are not functioning correctly is today impossible Furthermore, from our knowledge of neurological function, there are unequivocal indications that lesions or developmental defects in different parts of the central nervous system may lead to identical or at least very similar clinical pictures. However the cerebellum and, especially the cerebellar vermis, seems to be of particular importance.

Regarding symptoms and signs apart from *those concerning equilibrium and coordination*, parts of the *cerebral cortex* must be considered. Disturbance of the auditory perception corresponds to dysfunction of the temporal lobe or associated pathways. Defects of the frontal lobe could explain the mental retardation, as well as the marked lack of initiative and the emotional lability

To *summarize* the above discussion, it is obvious that in order to explain all the signs of the multifacetted clinical picture of the dysequilibrium syndrome, widespread developmental defects or lesions on different functional levels of the brain must be considered. Thus, even if the dysequilibrium syndrome is clinically well delineated in its typical cases, it is neither a neuropathological nor an etiological entity

C. *The Dysequilibrium Syndrome in relation to the Concept of Ataxic Cerebral Palsy*

In clinical medicine disagreement is never more eternal and pronounced than in discussions concerning classification. Classification within the concept of cerebral palsy does not constitute any exception—on the contrary In the 1st International Study Group on Child

Neurology and Cerebral Palsy in Oxford, September 1958 a British group presented for discussion the Little Club Memorandum on Terminology and Classification of Cerebral Palsy (54), which was the result of 1½ years of intensive attempts to obtain an internationally agreed system for definition of terms and syndromes. This has given rise to a lively discussion which has proceeded through the years. *A committee of the World Commission on* Cerebral Palsy has struggled with these classification problems since 1963 without any new relevant aspects apparently coming forth Points of disagreement are overwhelming. The main reason for this is certainly that cerebral palsy is not a scientific concept, but a concept created for practical purposes. One of the few things upon which definite agreement has been reached is the view that a classification still seems to be best based on clinical signs rather than on possible causes or sites of damage (10) This is due to our incomplete state of knowledge of causes and neuropathological changes resulting in the clinical pictures in question. Neurophysiological classifications have also been constructed (66) but have never been found to be useful tools for communication in daily clinical work.

Among the syndromes within cerebral palsy the classification of dyskinetic clinical types has attracted major interest during the last two decades, while ataxic forms have been discussed less frequently as regards their definitions, delineations and subgrouping Yet, ataxic forms of cerebral palsy seem to be much more common than originally believed (49) Research contributions from recent years concerning ataxic cerebral palsy are practically exclusively to be found in the works of Ingram (44 45 46 48 49)

Since Freud s description (26 27) of the first congenital and non-progressive cases of ataxia, the term ataxia as a heading for the type of syndrome present seems to have been used without thorough delineation in all those patients where unsteadiness and/or incoordination of the limbs with tremor have dominated Slow motor development, some degree of hypotonia and defective speech have been additional characteristics.

From the introductory discussion in chapter II and in this chapter ataxia as a neurological *sign* apparently must be differentiated from the much broader term ataxia" as a collection of *syndromes* within cerebral palsy The sign ataxia *sensu stricto* means dyssynergia in the *form of intention tremor dysmetria, etc. in* voluntary movements. The numerous syndromes within ataxic cerebral palsy" are much more difficult to delimit. The authors of the Little Club Memorandum realized this problem and were therefore apparently forced to define ataxic cerebral palsy only by exclusion an incoordination which is not to be attributed purely to dystonia, weakness or choreic movements" They also excluded any ataxia due to spinal disorder The same approach by exclusion was also used for definition by one of the authors in an earlier paper (39)

Dysequilibrium as a neurological sign is not equivalent to ataxia as a sign in its strict neurological definition. A lack of equilibrium has often been regarded as synonymous to "truncal ataxia which has been criticized by Marshall (60) We quite agree with this author that truncal ataxia is an unsuitable name in that it suggests that the disability is confined to the trunk, while, in fact, it is the equilibrium as a whole that is disturbed. In addition, it should be pointed out that ataxia in its strict sense is not evident until movement is attempted, while dysequilibrium mainly is a defect in the system of postural mechanisms.

It is true, however that probably all cerebral palsy patients with a syndrome dominated by a lack of normal equilibric sense, as described in this series, also have some—even if minimal—component of dyssynergia with tremor in their hand movements, i.e. they are at the same time ataxic. This ataxia may be of varying degrees, with all transitional forms from states with almost invisible intention tremor to those in which the dyssynergia becomes as ob-

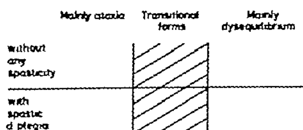


Fig 20 Schematic illustration of subgroups of ataxic cerebral palsy according to the dominance of the signs ataxia or dysequilibrium, on the one hand, and to the presence or absence of spastic diplegia, on the other

vious as the dysequilibrium. Thus the dysequilibric and the ataxic components often occur together but they are not synonymous qualitatively They should be recognized as separate clinical signs with probably different pathogenetic mechanisms, and demanding a somewhat different approach for clinical penetration and management.

The broader clinical concepts the syndrome of congenital cerebellar ataxia and the dysequilibrium syndrome as defined in chapter II imply for the patients not only the neurological signs ataxia and dysequilibrium in different degrees of distribution but also other characteristic and important components of cerebral dysfunction. As pointed out in previous chapters this applies particularly to patients with the dysequilibrium syndrome where associated characteristic stages of delayed motor development, a peculiar form of speech abnormality and severe perceptional disturbances are the rule The whole picture has been found to be so characteristic in most cases that it is tempting to delineate the dysequilibrium syndrome as a special entity distinct from the commonly used concept of "ataxic cerebral palsy" which is not a very adequate term. This view is strengthened by the fact that the ataxic signs in some of the patients are extremely slight and sometimes even insignificant while the dysequilibric signs are pronounced and most handicapping. However the apparent existence of all transitional forms between the two syndromes makes it questionable whether such nosological isolation should be stressed too greatly

Thus, while ataxia and dysequilibrium should be distinctly separated as *signs* they might well both be included as *syndromes* under the wider concept of "ataxic cerebral palsy as defined by the Little Club Memorandum (54) Under this heading a "vertical" subdivision has already been made by Ingram in his separation of pure congenital ataxia without spasticity from ataxic diplegia with spasticity mainly in the legs. In addition, it now seems reasonable to add a horizontal" subdivision with reference to the neurological peculiarities characterizing the dysequilibrium syndrome, which also may appear in a diplegic form. An attempt at a schematic subdivision of the four syndromes within ataxic cerebral palsy according to these neurological parameters has been made in Fig 20

It may be asked if there is any practical usefulness for this separation in further subgroups We consider that there is Children with the dysequilibrium syndromes have a complex multifacetted clinical picture, a characteristic developmental prognosis and particular educational problems, and they need special emphasis on some aspects of management in a well integrated habilitation programme These children should, therefore be recognized as a distinct group

If a more detailed classification of cerebral palsy should appear in the future, ataxia as a denomination for one of the main headings of syndromes should, we consider be abandoned as illogical from the semantic aspect, and misleading. The question of independence for the dysequilibrium syndrome then ought to be reconsidered. At present, however we probably have to keep ataxia" as the rag-bag which it today is for hitherto incompletely differentiated syndromes of disturbed coordination.

D *Concluding Clinical Comments*

Early recognition of the syndrome depends more upon correct interpretation of abnormal

deviations of the developmental and behavioral pattern than upon neurological signs. Routine neurophysiological examinations and chemical laboratory tests cannot give any diagnostic aid. The demonstration of a small cerebellar vermis at encephalography supports the diagnosis but this examination is not always necessary Good help can be obtained from vigilant observation of perceptional defects, which are particularly severe in this syndrome Such defects are however very difficult to trace during the first years of life

Recognition of the special functional defects which constitute the syndrome is essential for understanding of the problem and for planning of a correct therapeutic approach.

The importance of early therapy for the final outcome can be discussed. However the fact that this type of brain dysfunction leads to particularly severe disabilities of developmental performance and behaviour emphasizes the necessity for starting integrated and well planned training programmes as soon as the diagnosis is suspected. Intensive specialized training seems to provide the prerequisites of easier crossing of important thresholds between different developmental stages, thresholds which constitute insurmountable difficulties for the unaided child.

Faced with a non-verbal, inconsistent, withdrawn easily distractible, perseverating child, it is difficult to decide whether any one component of the child's handicap should have priority with regard to therapy For many years of the child's life, formal testing is usually not possible Therapeutic planning has to be based upon repeated informal testing of the child's approximate maturity levels in group activities with other children. When combined in an individual diagram, the summarized observations reveal progress but also a general state of immaturity During the first ten years of life the sensory motor and verbal development are so interrelated and interdependent that, in our opinion, the therapy should not be split up too much A multidisciplinary approach in which each member of the therapeutic team stresses his own field but has an open mind for all other aspects of the child's handicap will, in our experience, lead to higher conceptual thinking on the part of the child and, hence, to his educational and social progress.

CHAPTER IX

SUMMARY

The dysequilibrium syndrome, defined as a non-progressive neurological condition dominated throughout childhood by incapability of or pronounced difficulty in maintaining an upright body position and in experiencing the position of the body in space was investigated in a series of 13 patients. They were studied during various developmental stages in the years 1956–68 when at different ages (1–20 years) and again at a planned follow up investigation in 1969 This follow-up included a motor age test, neurological, ophthalmoneurological, otoneurological and audiological examinations, neurophysiological studies comprising EEG EMG nerve conduction velocity rates and muscle vibration reaction air-encephalography in certain cases, various intelligence, perception and body image tests, and finally a basic metabolic screening of the urine

A very peculiar and characteristic disturbance of the motor development and a distinct neurological syndrome were revealed The motor development, starting in a stage of pronounced inactive floppiness, was markedly retarded, and independent walking was usuall not achieved before about 9 years of

if at all. Four developmental stages were delineated. Stage I (floppy inactivity) with a mean duration of 3–4 years stage II (crawling) with a mean duration of 2–4 years, the average age for this stage being 3–7 years stage III (standing) lasting for at least 2–3 years and in the best cases, stage IV (walking independently 200 m or more)

The main neurological disorder was a markedly defective postural function and hence disturbed equilibrium In addition, signs of dyssynergia, mainly tremor and dysmetria were present to a minor extent in all patients. An age-dependent muscular hypotonia was regularly encountered as the third cardinal sign. Slight spasticity in the lower extremities was observed in only 3 patients. Convergent squint was present in 6 and cataracts in 3 patients. Mental retardation was common, only 4/13 being intellectually normal or only slightly subnormal. Pure tone audiograms were normal, as also was the peripheral vestibular function A severe and characteristic delay of language development was always present On basis of observations made, this delay was regarded to be principally due to a limited auditory memory Studies of visual perception revealed severe dysfunction in different areas, limiting their progress in education.

The EEG and nerve conduction velocity examinations gave normal results except for the findings in 2 patients with epilepsy whose EEGs showed epileptogenic activity The EMG findings were non-contributory Vibration studies revealed abnormal falling reactions, suggesting faulty central integration of the proprioceptive afferent impulses. Pneumoencephalography in 5 patients of this series and in a few additional patients studied later gave *heterogeneous results. A few children showed* a normal encephalogram, the majority of changes indicating cerebellar atrophy or hypoplasia, in some cases affecting only the vermis, but in other cases also the cerebellar hemispheres.

The dysequilibrium syndrome as presented in this series of cases is considered to be due to different prenatal causative factors, among which genetic disturbances are thought to be of certain importance. In our opinion, widespread brain lesions or developmental defects on different functional levels should be kept in mind in discussions of the pathophysiology of this multifacetted syndrome Clinical differentiation from the traditional "syndrome of congenital cerebellar ataxia" is made The existence of transitional forms between the two syndromes is admitted, making a clear-cut delineation and classification difficult. In earlier literature, cases apparently well consistent with the clinical syndrome described here have been classified under different headings, mostly as cases of Foerster's atonic-astatic syndrome" a concept which is discussed.

The therapeutic approach in the four different stages is presented in detail. It is emphasized that close integration of the different sections of therapy and training in a cerebral palsy unit is of particular importance for this group of patients. A very early start of intensive training is felt to be invaluable for these patients in helping them to overcome developmental thresholds.

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University of Turku, Turku, Finland

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CONTENTS

INTRODUCTION

Rheumatoid arthritis belongs to the group of connective tissue disorders, which is characterized by certain pathological changes in the connective tissue (13, 97 98). Each of these diseases can affect many organs in the body and renal involvement is one of the most common. It can be observed very frequently in systemic lupus erythematosus (44, 53 74 77 80 196) polyarteritis nodosa (6 25 35 145) anaphylactoid purpura (7 40 52, 101) and progressive systemic sclerosis (20, 43 112, 143, 182) but less frequently in dermatomyositis (43 53, 54, 55) and rheumatoid arthritis (12, 28 62, 138, 146) Renal changes in adult patients with rheumatoid arthritis (RA) have been reported earlier in many thorough studies (14 31 10 131 173) however systematic examinations of the incidence and quality of renal involvement in juvenile rheumatoid arthritis (JRA) have been only unsatisfactorily carried out. Nevertheless, it has been observed in studies examining the prognosis in juvenile rheumatoid arthritis that *uraemia is very frequently the primary cause* of death, in as many as 50 per cent of the cases (10 103) Thus previous studies do not give sufficient information about the type of juvenile rheumatoid arthritis in which renal changes develop, when they appear what the histopathological picture is, and how they connect with drug treatment. Possible renal lesion, however is significant for the prognosis of the patient and above all, safe treatment. Therefore it is important to clarify the incidence and quality of renal lesions in rheumatoid arthritis in children who are thoroughly examined and controlled. As for the fundamental examination of rheumatoid arthritis, children are preferable to adults because the changes due to age and cardiovascular diseases are lacking.

The writer had an exellent opportunity to perform the examination at the Children's Hospital, University of Turku, where both the basic examination and controls of a great proportion of children with rheumatoid arthritis in Finland have been concentrated.

RENAL INVOLVEMENT IN CHILD AND ADULT PATIENTS WITH RHEUMATOID ARTHRITIS

Proteinuria and pathological sediment findings

JRA patients

Until now the information of pathological urinary findings has come from general reviews of JRA, which are usually retrospective. Thus, part of the temporary pathological changes may have escaped notice. In these studies the reported frequency of proteinuria varies from 3 to 12 per cent (9, 12, 45, 62, 76, 103, 114, 150). In juvenile rheumatoid arthritis, nephrotic syndrome has only been reported in connection with amyloidosis (9, 147, 148, 160). The frequency of haematuria reported in various general reviews varies from 3 to 8 per cent (12, 42, 62, 116). It has usually been either temporary in connection with gold treatment (24, 161) or permanent, in connection with renal amyloidosis (147, 148, 160). Approximately one fourth (10) or a half (61) of the reported haematuria cases have been related to gold treatment. It has been pointed that leukocyturia or cylindruria occur in connection with amyloidosis (10, 147, 148).

Only a few more exact studies have been made on renal involvement in juvenile rheumatoid arthritis. Dumnova *et al* (59) observed pathological urinary findings in 30.8 per cent of the patients in their material of 296 patients. The findings occurred most frequently in patients with other extra-articular manifestations, too. However the changes were temporary in 25.8 per cent and permanent in only 5.0 per cent of the cases. Amyloidosis was observed in all the patients with persistent pathological urinary findings. Proteinuria occurred in 9.9 per cent of the material; in the other cases erythrocytes, leukocytes or cylinders were found in the urine. Anttila *et al* (10) reported forty-seven patients suffering from some kind of chronic nephropathy among 638 patients with juvenile rheumatoid arthritis. Thus, 7.4 per cent of the total material had distinct nephropathy. Only persistent pathological renal changes had been included in this study. Persistent proteinuria occurred in 7 per cent and persistent haematuria in 3 per cent of the total material. In the nephropathy group proteinuria occurred in 92 per cent, and haematuria in 38 per cent. Leukocytes and cylinders were observed in 45 per cent, temporary glucosuria in 12.8 per cent, and urinary tract infections in 36 per cent of the patients at some stage of the disease.

RA patients

Among adult patients the reported frequency of proteinuria varies from 7 to 50 per cent in various studies (5, 31, 139, 157, 173, 179). The frequency of persistent proteinuria reported in regular *systematic examinations* (60, 156, 173) varies from 7 to 12 per cent, and the frequency of cylindruria from 1 to 13 per cent.

Renal function

JRA patients

Systematic renal function studies in JRA patients have so far as I know been carried out

only by Dumnova et al. (59). In addition to this, renal function determinations have also been made in selected nephropathy or amyloidosis series (10, 147, 148, 195). Dumnova et al. determined endogenous creatinine clearance in 69 JRA patients in whom a distinct decrease (< 86/ml/minute) was observed in 24 children or in 34.8 per cent. However, in some of the cases the pathological finding was temporary and a persistent change was only observed in 13.0 per cent. Temporary changes accumulated in the early stage, while the disease was active. All of the patients with persistent change, had either proteinuria or pathological sediment findings. The percentage of pathological changes observed was highest in patients with other extra-articular manifestations, too. In the material concerned, renal concentration capacity had decreased in 16 per cent of the patients, but the decrease was permanent in only 13.5 per cent.

In their above-mentioned nephropathy material Anttila et al. observed decreased creatinine clearance in 23 per cent and decreased concentration capacity in 34 per cent of the patients (10). However, the studies had been carried out at very different stages of disease, in some of the cases at the onset of proteinuria, and in some of the cases later on. In the material concerned, serum creatinine or Urea N had increased in 15 per cent of the patients, generally when the disease approached its terminal stage.

Renal function variation has also been observed in patients with amyloidosis. In some cases, renal function tests were normalized at a better stage of disease, when the activity was lower (147).

RA patients

Several renal function studies in adults have been carried out with exactly controlled patients. Endogenous creatinine clearance has been examined most, and it has been observed to have decreased in 20—50 per cent of the patients (5, 31, 81, 107, 131). The most extensive studies of endogenous creatinine clearance changes in RA patients were carried out by Sørensen (171, 172, 173). His series consisted of 244 rheumatic patients and, in addition, a control group of 247 patients. He found that the patients with severe stages of RA had significantly lower creatinine clearance than those with milder stages, but there were no differences between those suffering from the milder disease and the control group. No relation was found between renal function and duration of the disease, but it had a significant relation to the activity of the disease as measured by the sedimentation rate. Nor could he observe any connection between medical treatment and decreased clearance in different treatment groups.

Para-aminohippuric acid clearance was observed to be only moderately affected by Allander et al. (5), although some investigators reported it decreased in as many as 4_ per cent of the examined cases (81). Changes in concentration capacity have rarely been examined. It has been reported that renal concentration capacity was within normal limits (142) or decreased in approximately 10 per cent of the cases (131, 173).

The values for the phenolsulphonphthalein excretion test were reduced in approximately 30 per cent of the material consisting of 20 patients (131).

Morphological changes

JRA patients

In the literature there are only few studies which describe renal changes observed in biopsy or autopsy specimens of JRA patients. These studies are generally restricted to explanation of cases with amyloidosis (see chapter on Amyloidosis). However, Wilkoszewski et al. (195) reported a renal biopsy material of seven children suffering from JRA. The material was selective, however, because clinical signs of renal involvement, e.g. proteinuria had been observed in all these children. Renal amyloidosis was observed in two cases.

Glomerular changes were observed in all the patients. These changes were similar to those found in *subacute glomerulonephritis*, i.e. increased number of endothelial and epithelial cells. Furthermore, increased connective tissue round blood vessels was observed in one specimen. The tubuli were intact, except for hyaline drop degeneration of tubular cells observed in one case.

RA patients

— *Amyloidosis* (see page 11)

— *Glomerular changes*

In autopsy material, several investigators have observed that diffuse glomerulitis, described by Bell (21) is a typical renal lesion in patients with rheumatoid arthritis (5, 14, 68, 98 137) This was characterized by diffuse glomerular hypercellularity. Its frequency in these studies was observed to vary between 13 and 70 per cent. However in later renal biopsy examinations this finding could not be observed in any of the patients (31 131). Brun *et al* (31) carried out a quantitative cell nuclear count of the individual glomeruli in renal biopsies taken from 3? RA patients and from 11 healthy control patients. Cell density was the same in both groups and thus, diffuse glomerular hypercellularity could not be observed in patients with RA. Instead, it was possible to demonstrate quantitatively that the cell nuclei distribution in the glomeruli was irregular. They occasionally occurred in localized accumulations as a form of local glomerulitis. However in the material concerned, the finding was always connected with other structural changes. Therefore, this finding was not considered a lesion caused by primary disease but a secondary finding. Furthermore the finding concerned has also been described in normal subjects (23 131)

Pasternack *et al* (131) carried out renal biopsy in ?0 patients with RA and found local glomerulitis in 11 patients, but found similar changes in two out of 10 control patients with previous urinary infection. In local areas of the glomeruli there was seen mulation of PAS-positive material with an increased number of cell nuclei. The local glomerulitis was the only renal abnormality in four patients, but in seven patients it was combined either with interstitial or vascular changes. The investigators believed that this is perhaps an early pathological change of rheumatoid kidney although it is not specific. No connection could be observed between the finding concerned and drug treatment.

Some investigators have described a few cases in which there were findings typical of membranous glomerulonephritis (5 31) but these could be a result of two simultaneous diseases. Furthermore membranous glomerulonephritic changes have been observed with nephrotic syndrome associated with gold therapy (75 96 108, 185)

— *Vascular changes*

In autopsy series arteritis with perivascular cell infiltration or periarteritis with fibrinoid necrosis in the walls of the blood vessels has been described by many authors (16 34, 113 157 158 163) However no finding of arteritis could be observed in renal biopsy examinations (31 131) Instead, arteriosclerotic and arteriolosclerotic changes have been observed which, however were considered a manifestation of the ageing of the kidney (31 131) Similarly lesions in the intima of small arteries have been described in some biopsy studies (63) In addition to this, Pasternack *et al.* have observed the thickening of the arterioles in one young patient (possibly suffering from JRA) No other changes were observed in the renal biopsy specimen in this case (131)

— *Interstitial changes*

Chronic interstitial nephritis with interstitial cell infiltration consisting predominantly of lymphocytes and plasma cells, and often proliferation of the interstitial tissue with peritubular and periglomerular fibrosis has

been described by many authors in studies using both renal biopsy and autopsy series, where its share varies from 28 to 45 per cent (31 131). On the other hand this finding has not been observed in all biopsy examinations (139). It has been discussed in the above-mentioned studies whether this finding is non-specific, i.e. would these patients also suffer from simultaneous pyelonephritis, or would it be caused, say by toxic factors. Analgesic abuse is one of the aetiological factors in chronic interstitial nephritis (38 39 40 107 165). However the finding has also been observed in one young patient and no analgesic intake occurred anamnestically in this case (131).

A high incidence of renal papillary necrosis has been reported in patients with analgesic abuse. Its frequency has been observed to be approximately 70 per cent in various autopsy materials of rheumatic patients (41, 107). Papillary necrosis has not been reported in children probably because children are not usually given phenacetin. However salicylates may also cause a picture of interstitial nephritis (38 39). (See also chapter Drug treatment and renal damage)

Amyloidosis

JRA patients

Amyloidosis is not an unusual complication in JRA. Both Withman 1903 (194) and in the same year Spitzy (164) reported one autopsy case of amyloidosis affecting the kidneys in JRA. Numerous individual cases of amyloidosis in JRA patients (11 36, 88 147 148, 181) have been reported after that. The frequency of amyloidosis in different studies is observed to vary between 1.2 and 6.7 per cent (Table 1).

The above-mentioned series are very heterogenic, the diagnosis of amyloidosis has usually been made by the Congo red test or in autopsy. No systematic examinations for the observation of amyloidosis had been carried out.

Amyloidosis can already be observed at a fairly early stage, even 2 years after the onset of the disease (59 160) or comparatively late even after 20 years duration (160). However in the above-mentioned series it has usually been observed within 4—8 years after the onset.

Table 1. *Reported incidence of amyloidosis in JRA*

Authors	Total No. of patients	No. of patients with amyloidosis (per cent)	
Coss *et al.* (1946)	56	1	(1.8)
Barkin (1952)	45	3	(6.7)
Edström (1958)	161		(1.2)
Schlesinger *et al.* (1961)	100	1	(1.0)
Lindbjerg (1964)	75	3	(4.0)
Dunnova *et al.* (1963)	296	15	(5.1)
Smith *et al.* (1968)	359	16	(4.1)
Anttila *et al.* (1969)	638	10	(1.6)

In the light of the above-mentioned studies, proteinuria, in some cases haematuria, and often nephrotic syndrome belong to the clinical picture. Renal insufficiency chronic uraemia and death was the last result in most of the cases.

RA patients

The frequency of amyloidosis in the kidneys in adult autopsy materials varies from 6 to 60 per cent (14 68 71 72, 121, 179). In systematic renal biopsy studies with non-selective material the frequency is 5—14 per cent (5 31 139). On the other hand, in selective material with persistent or transitory proteinuria, the frequency of amyloidosis is as high as 71 per cent (64). Amyloidosis can also be observed in the kidneys, although no clinical renal symptoms have occurred in the patient (131).

Diagnostics and histological renal alterations in amyloidosis

The intravenous Congo red test was earlier used as the test for amyloidosis. The conclusions of many studies, however show that the

test will give false positive and false negative results (26 167) Nowadays the diagnosis of amyloidosis is more efficiently carried out by rectal gingival or renal biopsy It has been observed in extensive studies that in cases where amyloidosis is present, the kidneys are also affected in 93—100 per cent of the patients (26, 47 64 84 138 179) Amyloidosis can be demonstrated in the tissues by using methylviolet staining and Congo red staining in combination with a polarizing light techni que (144)

The deposits of amyloid may be located on one or both sides of the basement membrane usually on th inner surface of the capillary tuft Capillary loops expand and are filled with amyloid. Amyloid is also found in vas cular walls, mainly in the media and ad ventitia, in both small and large arteries and arterioles. Amyloid may also be seen round tubular basal membrane and this may lead to tubular atrophy Atrophic tubules with eosinophilic colloid" casts like those seen in chronic pyelonephritis are some-times observed. Amyloid accumulation and increased fibrosis with lymphocytic infiltra tion may be observed in the interstitium (64 138)

Renal cause of death

In the literature there are a few studies based on material dealing with causes of death in JRA patients. However if such as exist are taken together one can observe that uraemia is the cause of death in 38.5 per cent of the cases (Table 2) Amyloidosis was observed in 26.4 per cent of all the fatal cases, whereas in cases with the cause of death originating in the kidneys, amyloidosis was present in 68.5 per cent. Other kidney-based causes of death have been poorly reported in the literature and apparently autopsy had not been carried out in all the cases. Therefore, the percentage of amyloidosis may even be somewhat higher However in the above-mentioned series, chronic pyelonephritis, chronic glomerulonephritis, nephrosis and nephrosclerosis have been reported as the cause of uraemia (10, 17 4., 116)

In rheumatoid arthritis in adults, uraemia is the primary cause of death in 11—34 per cent of the cases, in 20 per cent on an average (41, 72, 102, 161 179) Thus renal lesion is the cause of death in approximately every fifth adult and every third child

Table 2. *Renal cause of death in patients with JRA*

Authors	Total No. of patients	No. of deaths due to prim. disease	Renal cause	Amyloidosis
Colver (1937)	49	12		1
Coss et al (1946)	56		1	1
Pickard (194)	35	3	1	1
Lockie et al. (1948)	28		1	—
Barkl (195.)	45	9	4	3
Sury (195)	151	9	3	1
Edström et al. (1957)	90	3	1	1
Lindbjerg (1964)	75	4	3	3
Ansque et al (1967)	105	3	—	—
Smith et al (1968)	359	21	7	7
Anttila et al (1969)	628	23	12	6
Total	1664	91	35 (38.5 %)	24 (26.4 %)

DRUG TREATMENT AND RENAL DAMAGE

Analgesics

Spühler and Zollinger described primary haematogenic chronic interstitial nephritis, which they considered to have a connection with the intake of analgesics (165). Since then, numerous studies have been published describing the renal changes caused by analgesics, i.e. phenacetin and acetylsalicylic acid (22, 38, 39, 40, 41, 90). Renal papillary necrosis (RPN) was also considered to occur during the latter stage of the disease. The mechanism of the intake of analgesics leading to renal lesion is still obscure. However, in the light of the above-mentioned studies, analgesics no doubt play a part in the production of lesions. It was a long time uncertain whether the lesion was really caused by analgesics, or was the change primarily bacterial, and the analgesic intake secondary. However, in animal experiments Clausen observed typical morphological changes in the kidneys, both in those receiving salicylates and in those receiving phenacetin (38). Furthermore, the changes were almost equally common in coli-inoculated and in groups not inoculated, which means that coli-inoculation is not a factor in the development of these changes. Clausen and Pedersen (41) found that the incidence of uraemia among their rheumatoid patients increased from 20 per cent in 1951—56 to 46 per cent in 1957—60; during the same period, renal papillary necrosis (RPN) increased from 7.7 to 36.5 per cent. This was thought to be caused by increased intake of analgesics containing phenacetin. Heavy intake of such drugs was noted in all the patients with RPN.

However, Sorensen found no correlation between consumption of analgesics and renal function as determined by creatinine clearance test in patients with RA (171, 173). Nevertheless, it was observed that interstitial nephritis caused by analgetics affected the concentration capacity slightly (183), but not all investigators have proved this (40).

Clausen and Harvald (39) investigated the effect of acetylsalicylic acid, phenylbutazone and acetanilid upon the kidneys in provocation experiments, by Addis-count method. It was observed that acetylsalicylic acid gives a larger number of red and white cells in the urinary sediment than the other drugs. Prescott (140) used a special staining method in investigating urinary sediment and noted an increased number of tubular epithelial cells and red cells, but no white cells during the administration of acetylsalicylic acid. The phenacetin medication increased the number of tubular cells but not the number of red or white cells.

Phenylbutazone

Phenylbutazone has been observed to affect renal function. Meiers and Wetzels (117) observed that it increased water absorption, as well as retention of sodium and chlorides. On the other hand, it does not have a noteworthy effect on glomerular filtration rate. Tubular reabsorption of uric acid is inhibited, as is the tubular secretion of para-aminohippuric acid, para-aminosalicylic acid and phenol red. Thus, it is apparent that the primary location of action of phenylbutazone is at the proximal tubular level.

In addition, phenylbutazone has been observed to cause microscopic, slight haematuria and proteinuria (62, 105, 141, 153). The material of Schulze-Rhonhof *et al.* (153) consisted of 127 children with juvenile rheumatoid arthritis who were given phenylbutazone. About one third of the patients developed slight microscopic haematuria. The above-mentioned authors could not observe any effect on renal function. The material of Laine *et al.* (105) consisted of 660 patients with rheumatoid arthritis who received phenylbutazone. Proteinuria and/or haematuria occurred in one per cent of the cases.

Phenylbutazone has also been observed to cause glucosuria, although the sugar metabolism is normal (141). In addition, some cases of acute renal failure due to the intake of

phenylbutazone have been described in the literature (115 124, 160) Histological changes mainly in the tubuli, and also necroses of vascular walls with thrombosis, and hyalinized glomeruli have been reported in these studies.

On the other hand, Lawson *et al.* (107) could not observe any connection between phenylbutazone intake and the histological renal changes in rheumatic patients in their autopsy material.

Gold salts

Gold treatment often results in proteinuria and haematuria, most frequently of comparatively mild and temporary nature (24, 69 151, 169) The frequency of proteinuria and haematuria reported in children varies from 4.5 to 17 per cent (24, 62, 151) However the above-mentioned studies are all retrospective studies no examination programme had been planned in advance, and therefore part of the temporary changes may have escaped notice.

Transitory proteinuria has been observed in connection with gold treatment in adult patients. The frequency varies from 15 to 50 per cent (69 161) Sundelin (169) observed longterm proteinuria in 1.5 per cent of all the 730 patients receiving gold treatment. It has also been observed that the proteinuria in those receiving gold more often occurs in the most severe stages of rheumatoid arthritis than in the milder stages. Haematuria has also been reported in adults in a few per cent of those receiving gold (69 161, 169)

Gold treatment has also been observed to lead to the onset of nephrotic syndrome in which membranous glomerulonephritis is the predominant lesion (50 75 96 108, 185) In addition, it has been observed to produce acute tubular necrosis accompanied by renal failure (50) Among others, Lee *et al* (108) have assumed that gold would be an antigenic stimulus promoting the development of the renal lesion.

Many investigators have observed that gold accumulates in the renal tissue and remains there for a long time (30 108) Among others, Brun *et al* (30) carried out kidney biopsies in 19 patients who had received gold treatment. In all these cases gold was found in the glomerular tuft. From a few hours to 2—3 days after an injection, gold was found in the proximal tubules and later in the distal tubules and interstitial tissue, where it could be demonstrated up to 28 years after the last injection

Corticosteroids and ACTH

The literature contains several studies in which it is suspected that corticosteroids may cause vascular changes (79 95, 158) Among others, Kemper *et al.* (95) observed panarteritis in approximately one fourth of the rheumatic patients receiving corticosteroids, but no cases with panarteritis were observed in patients not receiving corticosteroids. Other investigators could not observe any connection between corticosteroid treatment and vasculitis (16 32, 34, 163)

Corticosteroids have also been thought to cause amyloidosis in rheumatic patients. The literature contains a great number of reports on amyloidosis which has developed during corticosteroid treatment (10 34, 64 132, 178, 193) But amyloidosis has been described in rheumatoid patients also before the use of corticosteroids (64 71, 179) Tellum and Lindahl (179) presented an autopsy series consisting of 17 patients with rheumatoid arthritis who had renal amyloidosis, and none of those had received corticosteroids. Similarly Gardner (71) reported a 9.3 per cent frequency of amyloidosis in patients with RA who had not received corticosteroids, and a 14.8 per cent frequency in patients received this treatment. The difference was not significant. Nor could Smith *et al* observe any connection between amyloidosis and corticosteroid treatment in patients with JRA (160) However animal experiments have proved that cortisone and ACTH can elicit and accelerate the formation of amyloidosis in certain test situation (100, 177)

Corticosteroid intake measured by endoge-

nous creatinine clearance (171 173) has not been observed to affect renal function in patients with RA.

RENAL INVOLVEMENT IN OTHER CONNECTIVE TISSUE DISORDERS

Systemic lupus erythematosus (SLE)

Renal disease characterized by proteinuria, haematuria, and cylindruria is a very common manifestation in children with diagnosed SLE. In the literature the frequency of pathological urinary findings varies from 80 to 100 per cent (44, 74, 77 133). In children suffering from SLE, renal symptoms characteristically appear at an early stage of the disease (44, 77 133) but the symptoms may also appear later over a period of years (29). In adult patients, the frequency of clinical renal findings varies from 50 to 80 per cent in large series reported in the literature (57 58 80, 84, 138 196). Nephrotic syndrome has very often been reported in connection with SLE both in child (133) and adult series (57 58 138) in approximately 30 per cent of the patients with affected kidneys (58 138). The cause of death is reported to have originated in the kidneys in approximately 0 per cent of child patients (44) and in 25 to 60 per cent in adult patients with SLE (58 138). However histological renal changes are observed in 80 to 100 per cent in autopsy series (57 84 138).

Polyarteritis nodosa (PAN)

Polyarteritis nodosa has been reported to occur both in children and adults (3 6 25, 35, 94). Clinical signs, proteinuria, haematuria, and cylindruria have been reported in 70 to 100 per cent of those with the idiopathic form of PAN and in 100 per cent of the patients with hypersensitive angitis (6 15 138). In most of the cases, proteinuria is mild, and nephrotic syndrome is seldom observed (138). Increased blood pressure is common in the idiopathic form, but less common in the hypersensitive form (25 145). Renal failure is the most common cause of death in PAN the frequency in hypersensitive angitis is approximately 90 per cent and in the idiopathic form 50 to 60 per cent of the cases (15 138).

Scleroderma

Progressive systemic sclerosis (PSS) is extremely uncommon in children, whereas focal scleroderma is relatively frequently observed in children (79 105). Renal involvement has not been reported in focal scleroderma. Also in PSS clinical evidence of renal disease varies only from 4 to 15 per cent (65 109 112, 187). However a significant reduction of renal plasma flow is observable in most of the patients with PSS, but endogenous creatinine clearance is within normal limits (184). It is observed in autopsy or biopsy examinations that kidneys are affected in 40 to 50 per cent of the patients (136, 138). If significant renal lesion is observed, the progression is usually rapid, and death results within a few years. Malignant hypertension often occurs in these cases (70, 109 112, 136, 138).

Anaphylactoid purpura (AP)

Renal involvement is a frequent complication in patients with AP in as much as 90 per cent of the cases (0). However most of the series indicate the frequency of 20 to 60 per cent (6, 7 49 126, 134, 168 191). Haematuria, proteinuria sometimes even nephrotic syndrome occur as clinical symptoms during the acute phase, and sometimes also hypertension and oliguria (49 70, 126). Chronic nephritis develops on an average in 5 per cent of the patients with renal involvement (7 191). In some cases renal involvement may be rapidly progressive and death may result in a few months (52, 53).

Dermatomyositis

Renal manifestations are rarely present in dermatomyositis. However microscopic hae-

maturia, mild or moderate proteinuria accompanied by azotaemia have been reported in a few individual child and adult cases (43, 48, 53, 93 159) Histopathological changes in the kidneys have not generally been described in dermatomyositis, except in cases where the disease is associated with other connective tissue disorders. In these cases the changes are mainly similar to those in PSS (53 174)

CRYOGLOBULINAEMIA AND CONNECTIVE TISSUE DISORDERS

Cryoglobulins are serum protein fractions which reversibly precipitate in the cold This was first observed in connection with multiple myeloma (195) Since then cryoglobulins have been described in many other diseases, e.g chronic lymphocytic leukemia (154) lymphosarcoma (1) infectious mononucleosis (188) syphilis (190) and connective tissue disorders such as systemic lupus erythematosus (19 118, 190) polyarteritis nodosa (33 111, 165) rheumatoid arthritis (85 118) and purpura arthralgia rheumatoid factor syndrome (27 119 190) The patients suffering from abovementioned diseases with the exception of myelomatoses have in their circulation a distinctive type of mixed cryoglobulin composed mainly of IgM and IgG immunoglobulins (66 118 190)

Anaemia, hypergammaglobulinaemia, anti nuclear antibodies, rheumatoid factor and depression of serum complement levels are often observed in adult patients with purpura arthralgia rheumatoid factor syndrome associated with cryoglobulinaemia (118 119)

Some of the patients with cryoglobulinaemia have developed a diffuse proliferative glomerulonephritis (67 119 109) manifested by hypertension proteinuria and haematuria. This renal lesion often progresses rapidly and leads to death.

It has been suggested that the cryoglobulins, which may well represent antigen antibody complexes, may become deposited within glomeruli to produce glomerulonephritis and also in small blood vessels to produce vasculitis (78, 118 176) It has been thought, especially in connection with SLE patients with glomerulitis, that mixed cryoglobulins containing complement components possibly play a role in the pathogenesis of glomerular lesion (51, 78, 176) The deposition of IgM and IgG as shown by immunohistological studies (8, 37 51) in the target tissues is compatible with this concept.

Histological renal findings are characterized by swelling and proliferation of intracapillary cells with mild to moderate neutrophil infiltration in the glomeruli. In addition, slight to moderate increase in basement membranelike material is observable generally in axial regions. In some cases necrotizing arteritis involving small and medium-sized arteries is observed in the kidneys. These were characterized by fibrinoid necrosis of the media with only mild inflammatory cell infiltration (118)

OUTLINES OF THE PRESENT STUDY

The purpose of the present clinical and histopathological study was

1. To study how frequently involvement of the kidneys occurs in juvenile rheumatoid arthritis.
2. To describe the morphological renal changes in juvenile rheumatoid arthritis.
3. To study whether the observed pathological urinary findings, decrease of renal function, increased blood pressure and pathological renal biopsy findings are correlated both with each other and with the following variables
   - clinical picture duration, activity and stage of the disease
   - functional capacity of the patients
   - existence of rheumatoid factor anti nuclear antibodies, positive cryoprecipitation reaction and hypergammaglobulinaemia.
4. To study whether the observed pathological findings are due to juvenile rheumatoid arthritis or its drug therapy

MATERIAL AND METHODS

Patients

The material consisted of 165 children with juvenile rheumatoid arthritis, treated at the Children's Hospital, University of Turku, in the years 1967—1970

All patients fulfilled the following diagnostic criteria of JRA (104)

1 Joint symptoms with onset before the age of 15
2. Swelling or limited mobility of two or more joints.
3. Continuous duration of joint symptoms for at least 3 months.
4 If only one joint involved histological synovial study was required for the diagnosis.
5 Elimination of other diseases of joints and connective tissue

The material was divided into two groups on the grounds of the existence of extra articular manifestations (Table 3) Joint symptoms alone occurred in 111 of the patients, one or more extra-articular manifestations were noted during the course of the disease in 54 children i.e in 32.7 per cent The frequency of different extra-articular manifestations in the total material was as follows iridocyclitis in 4 cases (14.5 %) myocarditis in 23 cases (13.9 %) pleuritis in 4 cases (4 %) pericarditis in 4 cases (2.4 %) rheumatoid rash in 16 cases (9.7 %) hepato- and or splenomegalia in 13 cases (7.9 %) lymphadenopathia in 13 cases (7.9 %) and fever accompanying in 32 cases (19.4 %) In addition, symptoms in the central nervous system were observed in one case and nonsuppurative peritonitis in one case.

Sex distribution in the material was as follows 121 (73.3 per cent) of the patients were girls and 44 (22.7 per cent) boys There was no significant difference between the sex distribution and the two forms of JRA (Table 3)

Table 3 *Classification of the patients*

Classification of the disease	Number of patients Girls	Boys	Total
JRA with joint symptoms only	85 (76.6)	26 (23.4)	111
JRA with extra articular manifestations	36 (66.7)	18 (33.3)	54
Total	121 (73.3)	44 (26.7)	165

The age at the onset of the disease is reported in Figure 1 No significant correlation between the two forms of JRA and the age at onset could be found.

The main serological findings are reported on Table 4 The rheumatoid factor was positive in 42 children (25.5 %) examined by Latex fixation test, and in 23 children (13.9 %) examined by Waaler Rose reaction (titre ≥1 64) No significant differences existed between the existence of rheumatoid

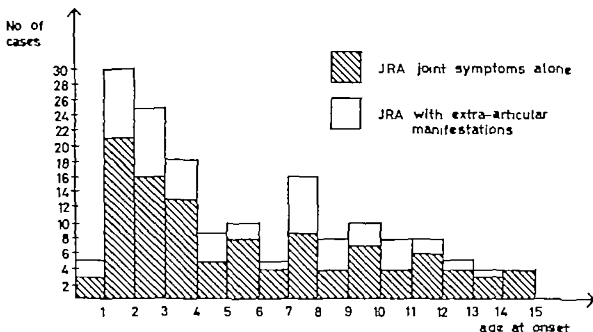


Fig 1 Age t onset of the disease.

Table 4. *The occurrence of rheumatoid factor (RF) antinuclear anti bodies (ANA) and cryoglobulins (Cr-glob) in the series*

Classification of the disease	No. f patients	Positive RF Latex No. (%)	W Ro No. (%)	Positive ANA No. (%)	Positive Cr-glob. No. (%)
JRA with joint symptoms only	111	25 (22.5)	14 (12.6)	39 (35.2)	18 (16.2)
JRA with extra articular manifestations	54	17 (31.5)	9 (16.7)	25 (46.3)	12 (22.2)
T tal	165	4_ (25.5)	23 (13.9)	64 (38.8)	30 (18.2)

factor and the JRA groups. Latex fixation test and Waaler Rose reaction were both positive in 12 patients. When comparing the titre values in the JRA groups, it could not be noted any differences.

Antinuclear antibodies (total titre 1 10—1 1280) occurred in 64 patients or in 38.8 per cent of the total material. Antinuclear antibodies were more often present, and the titre more often high (≥1:320) in patients with extra-articular manifestations than in those with joint symptoms alone However the difference was not significant [When comparing the titres with the standard serum, the 1 st International Reference Preparation of Anti-nuclear Factor serum (66/233) the titre 1 1280 corresponds to the titre 200 IU/ml of that.]

Cryoprecipitation reaction was positive (1—10 per cent) in 30 children or in 18.2 per cent of the patients. It was more often observed in patients with extra-articular

manifestations than in those with joint symptoms alone However the difference was not statistically significant There were no differences between the two JRA groups in quantitative determinations. Two patients without extra-articular manifestations showed positive LE cell phenomenon during the course of the disease but the controls later were negative Both patients had also low antinuclear antibody titre but cryoprecipitation reaction was negative JRA diagnosis was certain, however

The duration of the disease at the end of the observation time was, on average 3 years and 9 months, the range from 1 to 14 years. The duration of the disease varied from 1 to 3 years in 84 patients, from 3 to 7 years in 60 patients, and was over 7 years in 21 patients.

Controls

A group of 48 children admitted to hospital for examinations because of various psychic disorders, neurological symptoms, gastrointestinal symptoms or allergy served as controls in urinary examinations, renal function studies and blood pressure determinations. None of the patients had previously suffered from urinary infection or other renal disease At the time of examination they neither had any kind of infection nor had they received any drug therapy The age distribution varied from 2 to 5 years in 18 children, from 5 to 10 years in 14 children and from 10 to 15 years in 16 children

Twenty kidney specimens taken in autopsy were used as controls in histological examination (see page 44)

Methods

Follow up of patients

When each patient was first admitted to hospital, exact information of onset of the disease earlier drug treatment, previous diseases and development of the disease were registered. Thorough physical examination, especially locomotor status, laboratory and roentgenological examination were carried out on all the patients. Later the patients were controlled in the out patient department at —3 month intervals, even more frequently if required, and they were readmitted to hospital if the disease grew more serious. The clinical, laboratory and roentgenological examinations were controlled usually at every visit to hospital and some of these examinations were also controlled in the out-patient department (see later under the separate section headings)

Determination of the stage and functional capacity

Routine X ray examinations of hands, feet, and the affected joints were performed on all the patients. The changes were controlled at ½—1 year intervals. The technique described by Bolla was used in the radiological examinations of the joints (162)

The stage of the disease at various points of the disease was determined by using the following criteria (166):

Stage I (Early)

1 No destructive changes roentgenologically
2 Roentgenological evidence of osteoporosis may be present.

Stage II (Moderate)

1 Roentgenological evidence of osteoporosis with or without slight subchondral bone destruction; slight cartilage destruction may be present.
2 No joint deformities, although limitation of joint mobility may be present.
3 Adjacent muscle atrophy
4 Extra-articular soft tissue lesions, such as nodules and tenovaginitis may be present.

Stage III (Severe)

1 Roentgenological evidence of cartilage and bone destruction in addition to osteoporosis.
2 Joint deformity such as subluxation, ulnar deviation or hyperextension, without fibrous or bony ankylosis.
3 Extensive muscle atrophy
4 Extra-articular soft tissue lesions such as nodules and tenovaginitis may be present.

Stage IV (Terminal)

1 Fibrous or bony ankylosis.
2 Criteria of stage III.

Functional capacity f the patients t various stages of the disease was determined by using the following criteria (166)

Class I:

Complet functional capacity with bility to fulfil usual duties unhandicapped.

Class II

Adequat functional capacity for conducting nor mal activities despit handicap f discomfort or limited mobility of one or more joints.

Class III

Adequate functional capacity for performing few or none of the duties of the patients normal occupation or f ttending to his personal needs.

Class IV

Largely or wh lly incapacited with patient confined to bed or wheelchair permitting little or no ability t attend to personal needs.

General laboratory examinations

The following laboratory examinations were routinely performed with all the patient and controlled according t the progress f the disease t the hospital or out-patient department erythrocyte sedimentation rate (ESR) haemoglobin (46) Latex slide test (Hyland®) modified Waaler Rose reaction (4) C reactive protein (Hyland®) antinuclear antibodies by indirect FA technique using mouse liver cryostat section as substrat (187) and polyvalent anti-IgG and anti-IgM FITC conjugated sera (189) cryoprecipitation reaction (185) antistreptolysin O (86) antistaphylolysin (128) LE cells (46) paper lectrophoresis f serum protein (Beckman, Microzone®) and total serum protein (19*)

Kid ey examinations

Regular urinary examinations were performed on all the patient at —3 month intervals or more frequently t the hospital or out-patient department (see page 22) In ddition t this the Addi count method was used for the quantitative determination f erythrocyturia and leukocyturia (see page 22)

For the determination f renal function, the fol lowing methods were used endogenous creatinine clearance (C_{cr}) and true serum creatinine (Cr see page 30) phenolsulphonphtalein excretion test (PSP see page 32) concentration capacity (C_c) and dilution capacity (D_c see page 33) Blood pressure was regularly controlled t the hospital nd out patient department (see page 40)

An ttempt was made t perform percutaneous renal biopsy on every third JRA patient (see page 44) I ddition, renal specimens were taken in autopsy from patients who had died during the observation period.

The routine laboratory tests were performed in the Department of Clinical Chemistry th serological tests in the Department f Medical Microbiology and the X ray examinations in the Department f Radiology the Central Hospital, University f Turku. The anti nuclear tibodies were determined in the Municipal Bacteriological Laboratory Aurora Hospital, and in the Laboratory f Clinical Immunology Helsinki.

Statistical methods

The statistical calculations for comparison f the frequencies were performed by using one-tailed signi ficance test and the binomial test for one-sample cases. If the probability of error p was in the range $0.01 < p \leq 0.05$, the difference was regarded as nearly significant, if $0.001 < p \leq 0.01$ the difference was significant, if $p \leq 0.001$ the difference was highly significant.

Material and methods

Material

The material used in this longitudinal study was the above-mentioned total material i.e. 165 patients with JRA (see page 18). The urine samples were controlled many times at the hospital, and outpatient department at every visit usually at 2—3 months intervals. In addition, urinary protein of the patients receiving gold treatment (Myocrisin®) was controlled with every gold injection. The control material used in Addis count examinations was the same as that discussed above (see page 20).

Methods

Midstream urine specimens were taken, preferably in the morning from all the patients after careful washing of the genitals. Erythrocytes, leukocytes, epithelial cells, and cylinders were determined microscopically from the urine sediment. Urine bacterium cultivation and counts were performed either immediately from the fresh urine specimen, or by using first a slip slide method (Uricult®). In urinary sediment examination, over 3 erythrocytes, and over 5 leukocytes per field of vision were considered pathological. In the bacterial count over 100000 bacteria per 1 ml was considered the lower limit of infection (9*). If the finding was abnormal, the result was controlled, and, if required, confirmed by catheter urine specimen. In haematuria, bleeding status and coagulation status were also controlled, and cystoscopy was performed in some of the cases.

The Addis count method was used for quantitative determination of erythrocyturia and leukocyturia ( ). The test was performed only in the morning, when the patient was still in bed. Urine was collected for three hours, and the number of erythrocytes and leukocytes excreted in the urine in one minute was counted in the test. Erythrocyte excretion over 1000 erythrocytes/minute and leukocyte excretion over 2000 leucocytes/minute were considered pathological values.

Urinary protein and sugar were determined by using Albustix® and Clinistix® strips (Ames company). Positive results were controlled in the laboratory by using Biuret method (19*) for protein, and polarimetric method for sugar. Electrophoresis of urine protein was also carried out in some of the cases (18). Orthostatic test for provoking proteinuria was also performed in the cases with proteinuria.

Results

Pathological urinary findings

— Proteinuria

During the observation period, proteinuria occured at some stage of the disease in 70 cases, i.e. in 42.5 per cent of the JRA patients (Table 5). Twenty-eight patients had a short attack of proteinuria, but 42 patients or 25.5 per cent suffered from recurrent proteinuria. Persistent proteinuria only occured in four patients, i.e. 2.4 per cent of the JRA patients. The duration of proteinuria periods varied from a few days to four weeks. None of the patients developed nephrotic syndrome (total albumin of plasma < 2.5 g/l). The protein content of the urine varied usually from 0.5 to 3.5 g/l. In 18 cases urine protein was examined electrophoretically and proteinuria was observed to be nonselective i.e. different protein fractions of serum were found in the urine.

— Erythrocyturia

During the observation period erythrocyturia was found in 38 cases or in 23.0 per cent

Table 5 *Frequency of pathological urinary findings related to the clinical picture of JRA*

Classification	No. of patients	Proteinuria No.	Proteinuria %	Erythrocyturia No.	Erythrocyturia %	Leukocyturia No.	Leukocyturia %
JRA with joint symptoms only	111	40	36.1	[illegible]	24.3	29	[illegible]
JRA with extra-articular manifestations	54	30	55.6	11	20.2	13	4.1
Total	165	70	42.5	[illegible]	23.0	42	23.5

of the JRA patients (Table 5) It was diagnosed either by sediment examinations or by the Addis count method. Thirty-one patients had only one period of erythrocyturia, the duration of which varied from few days to three weeks. Seven children had two or more periods of erythrocyturia. In two of these cases amyloidosis was observed, coagulopathia in one case and in four patients erythrocyturia was associated with gold treatment Erythrocyturia was not observed in the control material when using the Addis count method or examining urine sediment.

— *Leukocyturia*

During the observation period significant leukocyturia (urinary infection and impurities excluded by repeated miction or catheter samples) was observed in 42 patients or in 25.5 per cent of the JRA patients (Table 5) Leukocyturia was found by sediment examination, and confirmed in most cases by the Addis count method, in which the leukocyte count varied between 2000 and 93000 per minute In the control material the leukocyte count obtained by this method was under 1500 leukocytes/minute in all the cases.

Repeated periods of leukocyturia occurred in 10 children or in 6.1 per cent of the JRA patients. Two of these patients had amyloidosis. Only one period of leukocyturia, which varied from a few days to three weeks, occurred in the other 32 children.

— *Urinary infection*

Verified urinary infection was found either during the observation period or earlier in 19 patients, two of whom were boys and seventeen girls. The frequency of urinary infection was thus 11.5 per cent Proteinuria erythrocyturia and leukocyturia connected with the infections concerned are not included in the above-mentioned series of urinary analysis.

— *Glucosuria*

Glucosuria was found once or repeatedly during the observation period in 8 patients. However in four patients it was only observed by Clinistix strips® and the positive reaction may in these cases be caused by salicylates. Thus, significant glucosuria in the total material was observed in four patients or in 2.4 per cent. Glucose tolerance test was normal in all of these four patients.

— *Cylindruria*

Granular or hyaline casts were observed in the urine samples of 8 patients, two of whom had amyloidosis. All the patients also had proteinuria or pathological urinary sediment. The frequency of cylindruria was thus 4.8 per cent

Frequency of pathological urinary findings

— *Correlation to the clinical picture of the disease*

As Table 5 shows, the frequency of proteinuria was greater in the patients with extra-articular manifestations than in the patients with joint symptoms only The dif

f rynes is stati tically significant ($p < 0.01$) No significant liff rence was observed f r the occurrence of erythrocyturia an l leukocyturia

— *Correlation t the durati n of the disease*

When stu lying the whol mat rial at the en l of the obs rvation peric l it can be s n that the frequency of proteinuria cases accu mulat s accoruling t the luration of the lisease However the same corr lation could not be observed for the frequency of erythrocyturia an l leukocyturia (Table 6)

When stu lying the duration of the disease up to the tim when th path logical urinary finding was first noted it can be observed that most of the erythrocyturia an l leukocyturia cases became manifest during the first year of illness (Table 7) Also in the figures for proteinuria the largest percentage was appar nt during the first year or during the first three years of illness.

— *Correlati n to other clinical and laboratory findings*

Stage of th disease

As Table 8 shows, the majority of the pa tients belong l to stage I or II at the obser vation time of pathological urinary finding

Table 6. *Frequency of pathological urinary findings at the end of the observati n time*

Duratio of the disease	No. f patie t	Proteinuria No.	%	Erythrocyt ria No.	%	Leukocyturi No.	%
1—3 ears	83	3*	39.6	*0	23.0	32	38.6
— ears	61	—	41.0		11.—	8	13.3
>7 ears	1	13	62.0		9.5		9.5
Tot l	163	70	4—5	*	23.0	45	23.5

Table *Durati n of the disease up to the time when path logical urinary findings were first note l*

Duration of disease at the time of pathological findings	Prot i uria No.	%	Erythrocyturia No.	%	Leukocyturia No.	%
<1 yea	30	4—9	1	63.—	30	71.5
1—3 years	23	32.9	10	*1.4	6	14.3
3— ears	10	14 7	4	10.5	5	11.9
>7 ears	7	10.0	3	7.9	1	—3
Tot l	70	100 0	38	100.0	4	100.0

Tabl 8 *Frequ ncy of pathological urinary findings related to stage of d seas at follow up*

Stage	N f patients	Protein ria N	%	Erythrocyturia No.	%	Leukocyturia No.	%
I + II	14	53	39 5	32	21.5	37	25.—
III + IV	18	12	66.7	6	33 3	5	*7.8
T t l	163	70	4—5	38	23.0	42	23.5

However nearly significant correlation was observable with proteinuria, whereas no correlation was observed with erythrocyturia or leukocyturia. The correlation between proteinuria and progression of the disease is understandable because the frequency of proteinuria increased as the disease continued, and the patients with stage III or IV had had the disease for more than four years

Functional capacity

Most of the patients (i.e. 153 cases) had functional capacity corresponding to class I or II. Only 12 children belonged to class III or IV at the time of examination (Table 9) Thus the correlation between pathological urinary findings and functional capacity remains uncertain. However the frequency of proteinuria and erythrocyturia was higher in the group of class III and IV than in the former The differences are nearly significant ($p < 0.05$) No significant correlation was observed between the frequency of leukocyturia and functional capacity

Activity of the disease

Erythrocyte sedimentation rate (ESR) haemoglobin (Hb) and occurrence of C-reactive protein (CRP) were used to describe the activity of the disease The highest average level of ESR and lowest average level of haemoglobin were chosen as criteria with which other values could be compared and correlated. Usually the values concerned show also the average level of ESR and Hb at the moment the pathological finding was observed.

As Table 10 shows, proteinuria erythrocyturia and leukocyturia were significantly more frequent in patients with high ESR values. The difference is highly significant in all groups ($p < 0.001$)

The same can be observed with haemoglobin values. Proteinuria and erythrocyturia were significantly more frequent in patients with low haemoglobin, compared to patients with higher haemoglobin values. The difference is highly significant ($p < 0.001$) In contrast, the same correlation could not be observed with the leukocyturia figures (Table 11)

Significant correlation was also observed between occurrence of proteinuria and positive CRP ($p < 0.01$) No significant correlations to CRP were found with erythrocyturia and leukocyturia (Table 12) On the whole obvious correlation was observed between the

Table 9 *Frequency of pathological urinary findings related to functional capacity at follow-up*

Class	No. of patients	Proteinuria No.	Proteinuria %	Erythrocyturia No.	Erythrocyturia %	Leukocyturia No.	Leukocyturia %
I+II	153	62	40.5	32	20.9	39	25.5
III+IV	12	8	66.7	6	50.0	3	25.0
Total	165	70	42.5	38	23.0	42	25.5

Table 10 *Frequency of pathological urinary findings related to mean sedimentation rate at follow up*

ESR (mm/h)	No. of patients	Proteinuria No.	Proteinuria %	Erythrocyturia No.	Erythrocyturia %	Leukocyturia No.	Leukocyturia %
< 50	111	36	32.5	21	18.9	20	18.0
> 50	54	34	63.0	17	31.5	22	40.7
Total	165	70	42.5	38	23.0	42	25.5

figures describing the activity of the disease and pathological urinary findings.

Rheumatoid factor

No correlation was found between pathological urinary findings and the existence of rheumatoid factor i.e. when rheumatoid factor is present, it does not indicate kidney disease. (Tables 13 and 14)

Antinuclear antibodies

The incidence of proteinuria was significantly higher in the group with antinuclear antibodies than in the group where they were absent ($p < 0.01$) but no correlation was found between antinuclear antibodies and the incidence of erythrocyturia or leukocyturia (Table 15)

Table 11. *Frequency of pathological urinary findings related to mean haemoglobin value at follow up*

Hb (g/100 ml)	No. of patients	Proteinuria No.	Proteinuria %	Erythrocyturia No.	Erythrocyturia %	Leukocyturia No.	Leukocyturia %
> 10	133	49	36.8	25	18.8	32	[illegible]1.0
< 10	32	[illegible]1	65.6	13	40.6	10	31.2
Total	165	[illegible]0	4[illegible]	38	23.0	4[illegible]	25.5

Table 12. *Frequency of pathological urinary findings related to C reactive protein (CRP)*

CRP	No. of patients	Proteinuria No.	Proteinuria %	Erythrocyturia No.	Erythrocyturia %	Leukocyturia No.	Leukocyturia %
Positive	61	34	55.7	13	1[illegible]	13	1[illegible]
Negative	104	36	34.6	[illegible]	[illegible]	[illegible]	[illegible]7.9
Total	165	70	4[illegible]	38	23.0	4[illegible]	[illegible]

Table 13. *Frequency of pathological urinary findings related to Latex fixation test*

Latex	No. of patients	Proteinuria No.	Proteinuria %	Erythrocyturia No.	Erythrocyturia %	Leukocyturia No.	Leukocyturia %
Positive	4[illegible]	20	47.6	1[illegible]	28.6	12	28.6
Negative	123	50	40.7	[illegible]	[illegible]	30	[illegible]
Total	165	70	4[illegible]	38	23.0	42	25.5

Table 14. *Frequency of pathological urinary findings related to Waaler Rose reaction (Wa-Ro)*

Wa-Ro	No. of patients	Proteinuria No.	Proteinuria %	Erythrocyturia No.	Erythrocyturia %	Leukocyturia No.	Leukocyturia %
Positive	23	11	47.8	5	1[illegible]	5	1[illegible]
Negative	14[illegible]	59	41.5	33	[illegible]	37	26.1
Total	165	70	4[illegible]	38	23.0	42	25.5

Cryoprecipitation reaction

Proteinuria occurred more frequently in the group with positive cryoprecipitation reaction, compared to the group with negative reaction (Table 16). The difference is highly significant ($p < 0.001$). The same could not be observed in the incidence of erythrocyturia or leukocyturia.

Correlation to drug treatment

— Proteinuria

Proteinuria was found in nine patients at an early stage of the disease before the drug treatment was commenced. Thus, proteinuria was in these cases apparently due to a renal lesion caused by the primary disease. In the same way it may be supposed that in the two patients with amyloidosis, proteinuria was due to renal lesion caused by the primary disease. Thus, proteinuria was with apparent certainty caused by primary disease in 6.7 per cent of the total material. In the other cases it was either due to medical treatment or primary disease.

When studying the possible part medical treatment plays in the occurrence of proteinuria it was observed that gold therapy (Myocrisin®) apparently provokes proteinuria in approximately half of the cases treated with gold. Gold treatment was given to 53 patients and 29 of these suffered from proteinuria during the treatment, i.e. 54.7 per cent of the cases. Proteinuria appeared in 48.3 per cent during the first year of treatment, in 37.9 per cent during the second and third year of treatment and in 13.8 per cent if the treatment had been given for more than 3 years.

On the other hand, excluding proteinuria cases related to gold treatment, it was impossible to find any correlation to the occurrence of proteinuria in connection with other drugs. Without paying attention to different combinations of treatment it was observed that proteinuria occurred in 33 patients out of 118 treated with antimalarial drugs (28.0 %), in 17 out of 58 treated with corticosteroids (29.3 %), in 19 out of 72 treated with phenylbutazone (26.4 %) and in 20 out of 72 treated with salicylates (27.8 %). In contrast, the difference in incidence of proteinuria in the patients treated with gold and those receiving some other kind of treatment was significant ($p < 0.01$).

Table 15. *Frequency of pathological urinary findings related to existence of antinuclear antibodies*

Antinuclear antibodies	No. of patients	Proteinuria No.	Proteinuria %	Erythrocyturia No.	Erythrocyturia %	Leukocyturia No.	Leukocyturia %
Present	64	36	56.2	14	21.9	16	25.0
Absent	101	34	33.7	24	23.8	26	25.8
Total	165	70	42.5	38	23.0	42	25.5

Table 16. *Frequency of pathological urinary findings related to cryoprecipitation reaction*

Cryoprecipitation	No. of patients	Proteinuria No.	Proteinuria %	Erythrocyturia No.	Erythrocyturia %	Leukocyturia No.	Leukocyturia %
Positive	30	21	70.0	9	30.0	8	26.7
Negative	135	49	36.3	29	21.5	34	25.2
Total	165	70	42.5	38	23.0	42	25.5

— *Erythrocyturia*

Erythrocyturia was observed in six patients at an early stage of the disease before the commencement of drug treatment. It is supposed that this finding was in these cases due to renal lesion caused by the primary disease. The same supposition can be made for three erythrocyturia cases of which two had amyloidosis and one coagulopathia. Thus, the primary disease can be regarded with apparent certainty as the reason for erythrocyturia in 5.5 per cent of the whole material. In the other cases the reason may be either drug treatment or primary disease.

Erythrocyturia was related to gold treatment in 9 out of 3 patients or in 1 0 per cent. In all the cases erythrocyturia was microscopical and disappeared when gold treatment was stopped. By regularly examining urinary sediment or by using the Addis count method, erythrocyturia was observed in 12 patients out of 80 receiving salicylates or in 15.0 per cent but only in 4 out of 87 patients or in 4.6 per cent treated with phenylbutazone. It was impossible to find any other correlations with drug treatment.

— *Leukocyturia*

Leukocyturia was observed in 10 cases (i.e. 6.1 per cent of the total material) before the treatment was commenced also at an early stage of the disease. Thus, it was apparently due to the primary disease. In the other cases either drug treatment or primary disease could have caused leukocyturia. When studying the frequency of leukocyturia in groups receiving different drugs no significant differences could be observed.

Discussion

In the material concerned more pathological urinary findings were observed than in earlier reports of JRA (10 50 61 103) in which only frequency of persistent proteinuria has usually been noted. On the other hand, fewer cases of persistent proteinuria were found in this study compared with earlier studies (9 10 103). This may be due to the low frequency of cases with amyloidosis in this material (1.2%). Pathological urinary findings were relatively frequently found at an early stage of the disease even before the commencement of drug treatment. Thus, the findings in question were apparently in these cases due to renal lesion caused by the primary disease. This is the first point which leads to the supposition that primary disease can lead to renal involvement.

Furthermore, a clear correlation was found between the figures describing the activity of the disease and the frequency of pathological findings. Similarly, a significant correlation was found between the pathological urinary findings and the existence of antinuclear antibodies, and positive cryoprecipitation reaction. It has been reported that high titres of antinuclear antibodies, and also positive cryoprecipitation reaction are found in systemic lupus erythematosus (18, 58 78, 110) and that renal lesion is connected with this disease in 70—90 per cent of the cases (44 58 74 113). Renal involvement is also reported in connection with cryoglobulinaemia (67 109). Thus, there is reason to suppose that renal changes also occur on this basis in some patients with JRA in whom the above-mentioned positive reactions are found. When explaining possible reasons for pathological urinary findings it is especially difficult to find out whether the finding in question is due to renal lesion caused by the primary disease or drug treatment. In addition it is difficult to find out which drug might cause this finding, because several different drugs were administered to the patients simultaneously. Furthermore drug treatment provoked a pathological finding only in some of the patients; thus, it is possible that the patient already had the lesion caused by the primary disease and as a result of drug treatment the lesion becomes manifest. However it is obvious that gold

treatment can lead to proteinuria and haematuria, as has also been observed earlier (4 62, 69 151, 169) In this study in which aurothiomalate (Myocrisin®) was used, the frequency of proteinuria and erythrocyturia was much higher than reported earlier (24 161) This may be because the control was carried out by close inquiry In addition, treatment with salicylates and phenylbutazone can cause haematuria (38 40 105) but the former causes haematuria significantly more often as observed in this study

ENDOGENOUS CREATININE CLEARANCE AND SERUM CREATININE

Material and methods

Material

The material in the kidney function test concerned consisted of 16_ children with juvenile rheumatoid arthritis, and 48 children who were at the hospital for some other reason (see page 2_). Three children under two years were excluded from the series analysed in this section because the kidney function may be immature until the age of two (140 197). Thus, the age distribution at the time of examination varied from two and a half to fifteen years (Table 17). Similarly two children who had previously suffered from prelonephritis were excluded from the study. Repeated examinations were carried out on 9_ children suffering from rheumatoid arthritis at different stages of the disease. True serum creatinine was measured both in connection with this test and at different stages of the disease at 6 to 12 monthly intervals.

Procedure. The patient received an ordinary hospital diet during the preceding days. The examination was carried out early in the morning after an overnight fast and the children were kept in bed during the procedure. Firstly the bladder was emptied and then the patient was given water to drink. The blood sample was taken after about one hour. The urine was collected for three hours, on average. The urine collection time to the nearest minute was recorded (83).

Creatinine determination: Plasma proteins were precipitated with trichloracetic acid and creatinine was absorbed from the protein free solution in Lloyd's reagent, from which it was extracted into alkaline picrate solution and the dye was measured (127). Urine creatinine was determined by making a dilution which corresponded to the diuresis and treating it like plasma. Using the standard points a straight line was plotted from which the results were read.

Table 17 *Age distribution of the JRA patients and controls. The frequency of pathological findings in renal function tests in different age groups*

Age (years)	Endogenous creatinine clearance		Phenolsulphonphtalein excretion		Concentration capacity	
	No. of JRA	No. of controls	No. of JRA	No. of controls	No. of JRA	No. of controls
3—6	48 (1_.5)	18 (—)	47 (18.5)	16 (—)	18 (22.2)	6 (—)
6—10	46 (6.5)	1 (—)	48 (16.)	1 (—)	46 (34.8)	9 (—)
10—15	66 (10.3)	18 (—)	63 (22_)	18 (—)	41 (31.7)	10 (—)
Total	163 (9.9)	48 (—)	133 (19.6)	46 (—)	103 (31.4)	25 (—)

( ) = percentage of patients with pathological findings

ENDOGENOUS CREATININE CLEARANCE AND SERUM CREATININE

Material and methods

Material

The material in the kidney function test concerned, consisted of 16[illegible] children with juvenile rheumatoid arthritis, and 48 children who were at the hospital for some other reason (see page [illegible].) Three children under two years were excluded from the series analysed in this section, because the kidney function may be immature until the age of two (149 197). Thus, the age distribution at the time of examination varied from two and a half to fifteen years (Table 17). Similarly two children who had previously suffered from pyelonephritis were excluded from the study. Repeated examinations were carried out on 9[illegible] children suffering from rheumatoid arthritis at different stages of the disease. True serum creatinine was measured both in connection with this test and at different stages of the disease at 6 to 1[illegible] monthly intervals.

Procedure: The patients received an ordinary hospital diet during the preceding days. The examination was carried out early in the morning after an overnight fast and the children were kept in bed during the procedure. Firstly the bladder was emptied and then the patient was given water to drink. The blood sample was taken after about one hour. The urine was collected for three hours, on average. The urine collection time to the nearest minute was recorded (53).

Creatinine determination: Plasma proteins were precipitated with trichloracetic acid and creatinine was absorbed from the protein free solution in Lloyd reagent, from which it was extracted into alkaline picrate solution and the colour was measured (127). Urine creatinine was determined by making a dilution which corresponded to the diuresis and treating it like plasma. Using the standard points, a straight line was plotted from which the result was read.

Table 17 Age distribution of the JRA patients and controls. The frequency of pathological findings in renal function tests in different age groups

Age (years)	Endogenous creatinine clearance		Phenolsulphophtalein excretion		Concentration capacity	
	No. of JRA	No. of controls	No. of JRA	No. of controls	No. of JRA	No. of controls
2—5	48 (12.5)	16 (—)	47 (19.5)	16 (—)	18 (22.3)	6 (—)
5—10	46 (6.5)	12 (—)	45 (16.7)	12 (—)	46 (34.8)	9 (—)
10—15	68 (10.3)	18 (—)	63 (22.[illegible])	18 (—)	41 (31.7)	10 (—)
Total	162 (9.9)	48 (—)	155 (19.6)	46 (—)	105 (31.4)	25 (—)

( ) = percentage of patients with pathological findings

ENDOGENOUS CREATININE CLEARANCE AND SERUM CREATININE

Material and methods

Material

The material in the kidney function test concerned, consisted of 16_ children with juvenile rheumatoid arthritis, and 48 children who were at the hospital for some other reason (see page 2_) Three children under two years were excluded from the series analysed in this section because the kidney function may be immature until the age of two (149 19_) Thus, the age distribution at the time of examination varied from two and a half to fifteen years (Table 17) Similarly two children who had previously suffered from pyelonephritis were excluded from the study Repeated examinations were carried out on 9_ children suffering from rheumatoid arthritis at different stages of the disease True serum creatinine was measured both in connection with this test and at different stages of the disease at 6 to 12 monthly intervals.

Procedure: The patients received an ordinary hospital diet during the preceding days. The examination was carried out early in the morning after an overnight fast and the children were kept in bed during the procedure First the bladder was emptied and then the patient was given water to drink. The blood sample was taken after about one hour The urine was collected for three hours on average The urine collection time to the nearest minute was recorded (83)

Creatinine determination: Plasma proteins were precipitated with trichloracetic acid and creatinine was absorbed from the protein free solution in Lloyd's reagent, from which it was extracted into alkaline picrate solution and the dye was measured (127) Urine creatinine was determined by making a dilution which corresponded to the diuresis and treating it like plasma. Using the standard points a straight line was plotted from which the result was read.

Table 17 Age distribution of the JRA patients and controls The frequency of pathological findings in renal function tests in different age groups

Age (years)	Endogenous creatinine clearance		Phenolsulphonphthalein excretion		Concentration capacity	
	No. of JRA	No. of controls	No. of JRA	No. of controls	No. of JRA	No. of controls
2—5	48 (12.5)	18 (—)	27 (18.5)	16 (—)	18 (22.2)	6 (—)
5—10	46 (6.5)	1 (—)	45 (16.7)	12 (—)	46 (34.8)	9 (—)
10—15	68 (10.3)	18 (—)	63 (22.2)	18 (—)	41 (31.7)	10 (—)
Total	162 (9.9)	48 (—)	138 (19.6)	46 (—)	103 (31.4)	25 (—)

( ) = percentage of patients with pathological findings

ENDOGENOUS CREATININE CLEARANCE AND SERUM CREATININE

Material and methods

Material

The material in the kidney function test concerned, consisted of 16[illegible] children with juvenile rheumatoid arthritis, and 48 children who were at the hospital for some other reason (see page [illegible]) Three children under two years were excluded from the series analysed in this section, because the kidney function may be immature until the age of two (140 197) Thus, the age distribution at the time of examination varied from two and a half to fifteen years (Table 17) Similarly two children who had previously suffered from pyelonephritis were excluded from the study Repeated examinations were carried out on 9[illegible] children suffering from rheumatoid arthritis at different stages of the disease. True serum creatinine was measured both in connection with this test and at different stages of the disease at 6 to 1[illegible] monthly intervals.

Procedure: The patients received an ordinary hospital diet during the preceding days. The examination was carried out early in the morning after an over night fast and the children were kept in bed during the procedure Firstly the bladder was emptied and then the patient was given water to drink. The blood sample was taken after about one hour The urine was collected for three hours, on average The urine collection time to the nearest minute was recorded (83)

Creatinine determinations: Plasma proteins were precipitated with trichloracetic acid and creatinine was absorbed from the protein free solution in Lloyd's reagent, from which it was extracted into alkaline picrate solution and the dye was measured (127) Urine creatinine was determined by making dilution which corresponded to the diuresis and treating it like plasma. Using the standard points, a straight line was plotted from which the result was read.

Table 17 *Age distribution of the JRA patients and controls. The frequency of pathological findings in renal function tests in different age groups*

Age (years)	Endogenous creatinine clearance		Phenolsulphonphtalein excretion		Concentration capacity	
	No. of JRA	No. of controls	No. of JRA	No. of controls	No. of JRA	No. of controls
2—5	48 (1[illegible].5)	18 (—)	27 (18.5)	10 (—)	18 (22.2)	6 (—)
5—10	46 (6.5)	1[illegible] (—)	43 (10.7)	12 (—)	46 (34.8)	9 (—)
10—15	68 (10.3)	15 (—)	63 (22.2)	15 (—)	41 (31.7)	10 (—)
Total	162 (9.9)	48 (—)	133 (19.6)	46 (—)	103 (31.4)	25 (—)

( ) = percentage of patients with pathological findings

of the disease lessened. Thus the frequency of permanent pathological changes in the material concerned was 6 per cent. No pathological results were found in the control material.

Serum creatinine (Cr)

Values of true serum creatinine were under 1. mg/100 ml in all of the patients. However it is known that serum creatinine level is considerably lower in children than in adults, and varies in different age groups (101). If in each age group the upper limit of the range in healthy children is regarded as the maximum normal value slightly elevated values during the course of the disease were observed in 18 children or in 11.1 per cent of the patients (Table 19). Normal values, within the range for healthy children, were observed in all children in the control group. Nine children also had pathological C , the other children showed the increased value later on. The rise in serum creatinine level was slight, on an average 0.2—0.4 mg/100 ml. At a later stage serum creatinine was normalized in seven children thus in 11 out of 16 patients (6.8 per cent) it remained slightly elevated.

PHENOLSULPHONPHTALEIN EXCRETION TEST

Material and method

Material

PSP test was performed in 138 patients with JRA and in the 46 children who formed the control material (see page 20). Thus, in total, 184 children were examined (Table 17). The children under two years of age were excluded from the study because renal function may be immature up to the age of two (149) and in addition, it is difficult to achieve an exact collecting time of two hours with very young children. Another group excluded from this study was the patients with previous urinary infection which might have caused pathological results.

Method

Procedure. The test was performed early in the morning after an overnight fast. The children were kept in bed during the examination. At the beginning of the test the patients were given about 300—400 ml of water to drink. After 20 minutes the bladder was emptied and then 0.6 ml (for those aged —5 years) or 1.0 ml (for those over 5 years) of phenolsulphonphtalein solution was injected intravenously. The bladder was emptied after exactly two hours (83).

Laboratory determination: Phenol red was determined colorimetrically from the urine specimen. The urine sample was first alkalinized with NaOH (.5 M) and the intensity of red colour was measured. The percentage of phenol red excreted in the urine is the recorded result. Excretion of over 55 per cent during two hours is regarded as a normal finding.

Results

PSP was pathological in 27 children or in 19.6 per cent of the whole material whereas no pathological results were found in the control group (Table 17). The difference is statistically highly significant ($p < 0.001$). Pathological values varied from 35 to 55 per cent and normal values from 60 to 90 per cent. No statistical differences in the frequency of pathological results were observed in different age groups.

CONCENTRATION AND DILUTION CAPACITY

Material and method

Material

As shown in Table 17, renal concentration capacity and dilution capacity were defined in 105 patients with JRA and in 25 other children without anamnestic data of renal symptoms (see page 20). As above the age varied from two to fifteen years at the time of examination.

of the disease lessened. Thus the frequency of permanent pathological changes in the material concerned was 6.2 per cent. No pathological results were found in the control material.

Serum creatinine (Cr)

Values of true serum creatinine were under 1.2 mg/100 ml in all of the patients. However, it is known that serum creatinine level is considerably lower in children than in adults, and varies in different age groups (101). If in each age group the upper limit of the range in healthy children is regarded as the maximum normal value, slightly elevated values during the course of the disease were observed in 18 children or in 11.1 per cent of the patients (Table 19). Normal values, within the range for healthy children, were observed in all children in the control group. Nine children also had pathological C_{cr}, the other children showed the increased value later on. The rise in serum creatinine level was slight, on an average 0.2—0.4 mg/100 ml. At a later stage serum creatinine was normalized in seven children, thus in 11 out of 162 patients (6.8 per cent) it remained slightly elevated.

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PSP test was performed in 138 patients with JRA and in the 46 children who formed the control material (see page 20). Thus, in total, 184 children were examined (Table 17). The children under two years of age were excluded from the study, because renal function may be immature up to the age of two (149) and in addition, it is difficult to achieve an exact collecting time of two hours with very young children. Another group excluded from this study was the patients with previous urinary infection which might have caused pathological results.

Method

Procedure. The test was performed early in the morning after an overnight fast. The children were kept in bed during the examination. At the beginning of the test the patients were given about 300—400 ml of water to drink. After 20 minutes the bladder was emptied and then 0.6 ml (for those aged —3 years) 1.0 ml (for those over 3 years) of phenolsulphonphtalein solution was injected intravenously. The bladder was emptied after exactly two hours (83).

Laboratory determination. Phenol red was determined colorimetrically from the urine specimen. The urine sample was first alkalinized with NaOH (2.5 M) and the intensity of red colour was measured. The percentage of phenol red excreted in the urine is the recorded result. Excretion of over 55 per cent during two hours is regarded as a normal finding.

Results

PSP was pathological in 27 children or in 10.6 per cent of the whole material, whereas no pathological results were found in the control group (Table 17). The difference is statistically highly significant ($p < 0.001$). Pathological values varied from 35 to 55 per cent and normal values from 60 to 90 per cent. No statistical differences in the frequency of pathological results were observed in different age groups.

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Material and method

Material

As shown in Table 17, renal concentration capacity and dilution capacity were defined in 105 patients with JRA and in 25 other children without anamnestic data of renal symptoms (see page 20). As above, the age varied from two to fifteen years at the time of examination.

— Correlation to the duration of the disease

The kidney function tests gave pathological results even during the first year of illness, range 2 months to 11 months. This was apparent in all renal function tests (Table 21). When the duration of the disease exceeded 3 years, range 3 years to 13 years, the frequency of the pathological results somewhat increased. However the differences are not statistically significant in spite of the concentration capacity which was more often decreased when the duration of the disease was over 3 years, than when it was under one year. However the difference in this test is also only nearly significant ($p < 0.05$). High creatinine clearance values occurred in 80 per cent of the cases during the first three years.

— Correlation to other clinical and laboratory findings

Stage of the disease

When studying the possible correlation between the stage of the disease and decreased renal function, no correlation was observable (Table 22.) However the material is not really representative because majority of the patients belonged to stage I or II, and only a small proportion (11.5 per cent) to stage III or IV.

Functional capacity

As Table 23 shows, the incidence of pathological findings was somewhat greater in classes III and IV than in classes I or II. The differences, however are not statistically significant except for concentration capacity in which the difference is nearly significant ($p < 0.05$).

Activity of the disease

As above ESR, Hb and CRP have been used to describe the activity of the disease at the time of examination. Table 24 shows when ESR was over 50 mm/h, nearly significantly more pathological results ($p < 0.05$) were observed in determinating C_{cr} and PSP than in cases with lower ESR (under 50 mm/h). For

Table 22. *Frequency of pathological kidney function tests related to stage of the disease at follow up*

Stage	Endogenous creatinine clearance			Phenolsulphophtalein excretion			Concentration capacity		
	No. of patients	Path.val. No.	(%)	No. of patients	Path. val. No.	(%)	No. of patients	Path.val. No.	(%)
I+II	145	14	(9.7)	[illegible]	23	(19.0)	92	28	(30.4)
III+IV	17		(11.8)	17	4	(23.5)	13	5	(38.5)
Total	[illegible]	16	(9.9)	138	27	(19.6)	103	33	(31.4)

Table 23. *Frequency of pathological kidney function tests related to functional capacity at follow up*

Class	Endogenous creatinine clearance			Phenolsulphophtalein excretion			Concentration capacity		
	No. of patients	Path.val. No.	(%)	No. of patients	Path. val. No.	(%)	No. of patients	Path.val. No.	(%)
I+II	150	14	(9.3)	[illegible]	23	(18.5)	93	25	([illegible])
III+IV	1	2	(16.7)	14	4	(28.6)	12	8	([illegible])
Total	162	16	(9.9)	138	[illegible]	(19.6)	105	33	(31.4)

— *Correlation to the duration of the disease*

The kidney function tests gave pathological results even during the first year of illness, range 3 months to 11 months. This was apparent in all renal function tests (Table 21). When the duration of the disease exceeded 3 years, range 3 years to 13 years, the frequency of the pathological results somewhat increased. However the differences are not statistically significant in spite of the concentration capacity which was more often decreased when the duration of the disease was over 3 years, than when it was under one year. However the difference in this test is also only nearly significant ($p < 0.05$). High creatinine clearance values occurred in 80 per cent of the cases during the first three years.

— *Correlation to other clinical and laboratory findings*

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When studying the possible correlation between the stage of the disease and decreased renal function, no correlation was observable (Table 22.) However the material is not really representative, because majority of the patients belonged to stage I or II and only a small proportion (11.5 per cent) to stage III or IV.

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Table 22. *Frequency of pathological kidney function tests related to stage of the disease at follow-up*

Stage	Endogenous creatinine clearance			Phenolsulphonphtalein excretion			Concentration capacity		
	No. of patients	Path. val. No.	(%)	No. of patients	Path. val. No.	(%)	No. of patients	Path. val. No.	(%)
I+II	143	14	(9.7)	121	23	(19.0)	92	28	(30.4)
III+IV	17	2	(11.8)	17	4	(23.5)	13	5	(38.5)
Total	163	16	(9.9)	138	27	(19.6)	105	33	(31.4)

Table 23. *Frequency of pathological kidney function tests related to functional capacity at follow-up*

Class	Endogenous creatinine clearance			Phenolsulphonphtalein excretion			Concentration capacity		
	No. of patient	Path. val. No.	(%)	No. of patients	Path. val. No.	(%)	No. of patients	Path. val. No.	(%)
I+II	150	14	(9.3)	124	23	(18.5)	93	25	(26.9)
III+IV	12		(16.7)	14	4	(28.6)	12	8	(66.6)
Total	162	16	(9.9)	138	27	(19.6)	105	33	(31.4)

the determination of concentration capacity the difference is significant ($p < 0.01$)

Likewise, if haemoglobin was low under 10 g/100 ml, nearly significantly more pathological findings were observed in all renal function tests compared to the cases with higher haemoglobin values i.e. over 10 g/100 ml (Table 25)

When the incidence of pathological results was correlated with the existence of positive CRP it was observed that the concentration capacity was decreased in 54.8 per cent of the group with positive CRP but only in 21.6 per cent of the group with negative CRP (Table 26) The difference is highly significant ($p < 0.001$) In contrast, the same phenomenon could not be observed in the other renal function tests.

Thus, decreased renal function was proportionally more often observed when the disease was active than when it was less active.

Rheumatoid factor

As Tables 27 and 28 show no significant correlation was observed between the existence of rheumatoid factor and pathological creatinine

Table 24 *Frequency of pathological kidney function tests related to sedimentation rate (ESR) at follow-up*

ESR	Endogenous creatinine clearance			Phenolsulphonphtalein excretion			Concentration capacity		
	No. of patients	Path.val. No.	(%)	No. of patients	Path.val. No.	(%)	No. of patients	Path.val. No.	(%)
< 50 mm/h	98	5	(3.1)	88	13	(14.8)	63	14	(22.2)
> 50 mm/h	64	11	(17.2)	50	14	(28.0)	42	19	(45.2)
Total	162	16	(9.9)	138	27	(19.6)	105	33	(31.4)

Table 25 *Frequency of pathological kidney function tests related to haemoglobin (Hb) values at follow-up*

Hb (g/100 ml)	Endogenous creatinine clearance			Phenolsulphonphtalein excretion			Concentration capacity		
	No. of patients	Path.val. No.	(%)	No. of patients	Path.val. No.	(%)	No. of patients	Path.val. No.	(%)
> 10	131	10	(7.6)	110	18	(16.4)	84	23	(27.4)
< 10	31	6	(19.4)	28	9	(32.2)	21	10	(47.6)
Total	162	16	(9.9)	138	27	(19.6)	105	33	(31.4)

Table 26 *Frequency of pathological kidney function tests related to C reactive protein (CRP)*

CRP	Endogenous creatinine clearance			Phenolsulphonphtalein excretion			Concentration capacity		
	No. of patients	Path.val. No.	(%)	No. of patients	Path.val. No.	(%)	No. of patients	Path.val. No.	(%)
Positive	51	5	(9.8)	53	12	(22.6)	31	17	(54.8)
Negative	111	11	(9.9)	85	15	(17.7)	74	16	(21.6)
Total	162	16	(9.9)	138	27	(19.6)	105	33	(31.4)

clearance or PSP values. The concentration capacity was more often decreased in seropositive than seronegative group. The difference is significant ($p < 0.01$).

Antinuclear antibodies

Renal function tests were more often pathological in the patients with antinuclear antibodies, however the difference was significant only in connection with concentration capacity and nearly significant in connection with C_{Cr} (Table 29).

Cryoprecipitation reaction

Concentration capacity was more often decreased in the cryopositive than in the cryonegative group. The difference is nearly significant ($p < 0.05$). In contrast the same correlation was not found in the results for C_{Cr} or PSP (Table 30).

— *Correlation to drug treatment*

When studying the possible effect of drug treatment on decreased kidney function, the material was chosen so that in some of the cases renal function tests were carried out before the onset of treatment, at an early stage of the disease. As table 31 shows, C_c was pathological in 8.7 per cent, PSP in 14.6 per cent and Ce in 18.2 per cent of the patients

Table 27. *Frequency of pathological kidney function tests related to Latex fixation test*

Latex	Endogenous creatinine clearance			Phenolsulphophtalein excretion			Concentration capacity		
	No. of patients	Path.val. No.	(%)	No. of patients	Path.val. No.	(%)	No. of patients	Path. al. No.	(%)
Positive	4_	5	(11.9)	42	7	(16.7)	28	14	(50.0)
Negative	120	11	(9.1)	96	20	(20.8)	77	19	(24.7)
Total	162	16	(9.9)	138	*7	(19.6)	105	33	(31.4)

Table 28. *Frequency of pathological kidney function tests related to Waaler Rose reaction (Wa Ro)*

Wa Ro	Endogenous creatinine clearance			Phenolsulphophtalein excretion			Concentration capacity		
	No. f patients	Path.val. No.	(%)	No. of patients	Path. al. No.	(%)	No. of patients	Path.val. No.	(%)
Positive	23	3	(13.1)	31	5	(23.3)	16	9	(56.3)
Negati	130	13	(9.3)	117	23	(18.8)	89	4	(27.0)
Total	162	16	(9.9)	138	27	(19.0)	105	33	(31.4)

Table 29. *Frequency of pathological kidney function tests related to existence of antinuclear antibodies*

Antinuclear antibodies	Endogenous creatinine clearance			Phenolsulphophtalein excretion			Concentration capacity		
	No. of patients	Path.val. No.	(%)	No. f patients	Path. al. No.	(%)	No. of patients	Path. al. No.	(%)
Present	64	11	(17.2)	51	13	(25.5)	40	19	(47.5)
Absent	98	5	(5.1)	87	14	(16.1)	65	14	(_1.5)
Total	162	16	(9.9)	138	27	(19.6)	105	33	(31.4)

not receiving drug treatment. In these cases the decreased values in above-mentioned tests were apparently due to renal lesion caused by the primary disease.

Of the patients receiving drug treatment, C_{cr} was decreased in 10.8 per cent, PSP in 22.2 per cent and Cc in 41.0 per cent of the patients. No significant differences were observed between the groups treated or not treated when they were studied by C_{cr} or PSP methods, but concentration capacity was more often pathological in the group receiving drug treatment ($p < 0.05$). Thus, it is possible that drug treatment may have caused the decrease in the function test under discussion.

Twenty five per cent of the elevated Cc values belonged to the group not receiving drugs, and 75 per cent to the group which was treated.

When comparing the frequency of patho-

Table 30 *Frequency of pathological kidney function tests related to cryoprecipitation reaction*

Cryoprecipitation reaction	Endogenous creatinine clearance			Phenolsulphonphtalein excretion			Concentration capacity		
	No. of patients	Path.val. No.	(%)	No. of patients	Path.val. No.	(%)	No. of patients	Path.val. No.	(%)
Positive	30	5	(16.7)	30	5	(16.7)	16	9	(56.2)
Negative	13[illegible]	11	(8.3)	103	22	(20.4)	89	24	(27.0)
Total	162	16	(9.9)	138	27	(19.6)	105	33	(31.4)

Table 31 *Frequency of pathological kidney function tests related to drug treatment*

	Endogenous creatinine clearance			Phenolsulphonphtalein excretion			Concentration capacity		
	No. of patients	Path.val. No.	(%)	No. of patients	Path.val. No.	(%)	No. of patients	Path.val. No.	(%)
No treatment	69	6	(8.7)	48	7	(14.6)	44	8	(18.[illegible])
Treatment	93	10	(10.8)	90	20	(22.2)	61	25	(41.0)
Total	162	16	(9.9)	138	27	(19.6)	105	33	(31.4)

Table 32. *Frequency of pathological kidney function tests related to different therapy groups*

Therapy groups	Endogenous creatinine clearance			Phenolsulphonphtalein excretion			Concentration capacity		
	No. of patients	Path.val. No.	(%)	No. of patients	Path.val. No.	(%)	No. of patients	Path.val. No.	(%)
Gold	39	5	(12.8)	39	13	(33.3)	[illegible]5	9	(36.0)
No gold	54	5	(9.3)	51	7	(13.7)	36	16	(44.3)
Antimalarial drugs	73	8	(10.9)	73	16	(21.9)	49	17	(34.7)
No antimalarial drugs	20	2	(10.0)	17	4	(23.5)	12	8	(66.6)
Corticosteroids	42	5	(11.9)	39	12	(30.8)	27	11	(40.7)
No corticosteroids	51	5	(9.8)	51	8	(15.7)	34	14	(41.2)
Phenylbutazone	52	4	(7.7)	51	12	(23.5)	34	13	([illegible]8.2)
No phenylbutazone	41	6	(14.6)	39	8	(20.5)	27	12	(44.3)
Salicylates	33	6	(18.[illegible])	30	10	(33.3)	24	15	(62.5)
No salicylates	60	4	(6.7)	60	10	(16.7)	37	10	(27.0)
Whole series of JRA patients	93	10	(10.8)	90	20	(22.2)	61	[illegible]5	(41.0)

logical results in different therapy groups without paying attention to the drug combinations (Table 32) it could be observed that C_{cr} was more often pathological in the patients treated with salicylates (in 18.2 per cent) than in the patients not receiving salicylates (in 6.7 per cent). The difference is nearly significant ($p < 0.05$). The same correlation could be observed when comparing the group receiving salicylates and the group receiving phenylbutazone.

PSP was more frequently pathological in those receiving gold (Myocrisin®) than in the cases not receiving this drug. The difference is significant ($p < 0.01$). The situation was the same for salicylates when examination was carried out by means of the PSP test.

Co was more often pathological in patients receiving salicylates than in those receiving other drugs. However, the differences are only nearly significant ($p < 0.05$). Nevertheless, the difference is statistically significant ($p < 0.01$) when the group receiving salicylates is compared with the group not treated with salicylates.

When studying the possible effect of the duration of drug treatment on the incidence of pathological results, no correlations could be observed.

Discussion

In this study there were relatively few pathological creatinine clearance values, only in 9.9 per cent of the cases. On the other hand, this is understandable because the renal function reserves are large, and minor pathological changes do not appear in function tests. However, Dumnova *et al.* (59) observed pathological results in 35.0 per cent of their child material, although in part of the cases the change was temporary. The frequency of permanent changes was 13.0 per cent, which is somewhat higher than in this material (6.2 per cent).

In adult patients with rheumatoid arthritis, pathological results in C_{cr} test have been observed noticeably more frequently: in 36 per cent according to Sorensen (173) and in 47 per cent according to Heidelmann (81).

A few studies of PSP and rheumatoid arthritis have been published. Wilkoszewski *et al.* (195) reported that in 7 JRA patients with proteinuria and other signs of renal lesions, 5 patients had decreased PSP. Pasternack *et al.* (131) found decreased PSP in 30 per cent of 20 adult patients with rheumatoid arthritis, and none of these patients had proteinuria at the time of examinations. In this material pathological PSP values were observed in 19.6 per cent of the patients.

Concentration capacity was pathological in 31.4 per cent of the patients in the present study, which is a higher figure than those reported earlier in the literature. Dumnova *et al.* (59) observed pathological results in 16 per cent of the patients, and Anttila *et al.* (10) in 34 per cent of the JRA patients suffering from nephropathy. On the other hand, Sorensen found the concentration capacity to be within the normal limits in the adult material (173). Similarly, Pasternack *et al.* found pathological results in only 10 per cent of the adult RA patients (131).

The kidney function test results were more often pathological in patients with other extra-articular manifestations. However, the difference was statistically significant only in the C_{cr} test. Dumnova *et al.* found the same phenomenon.

A clear correlation could be observed between the activity and the incidence of pathological renal function tests in this study. Rostropowicz *et al.* (147) also found correlation at different stages of the disease between variations in renal function tests and the activity of the disease. Similarly, Sorensen (173) found a correlation between the activity or stage of the disease and pathological C_{cr} test. In this study there was no correlation between the pathological renal function tests and the stage of the disease.

Pathological results in renal function tests were observed in some of the patients even at

an early stage of the disease, before drug treatment was commenced. Thus, in these cases the pathological values are apparently due to renal changes caused by the primary disease. On the other hand, a correlation could be observed with the activity of the disease, which usually was highest at an early stage of the disease.

A correlation between the duration of the disease and decreased renal function was only observed in the figures for concentration capacity. Thus, it is possible that drug treatment is one factor in the decrease of renal concentration capacity.

It is difficult to define correlation between decreased renal function and drug treatment, because pathological results were observable even before the commencement of drug treatment. Thus, it is possible that decreased function observed later might stem from the same cause, although the patients had received treatment which might also have caused the change. On the other hand, it is possible that the already existing change in the kidneys becomes manifest as the effect of drugs. Furthermore, combined drug treatment makes assessment of the results more difficult. Nearly all available antirheumatic drugs may have been administered to one patient. However from indirect evidence it can be said that salicylates possibly decreased renal function. This was observed in all kidney function tests when comparing the different groups one with the other. Similarly, gold treatment might decrease tubular function, because PSP was more often decreased in patients who had received gold than in those who had not received gold. This is understandable, because gold may be found in tubular cells even years after gold treatment has been discontinued (30). However, the situation is not unambigous even in these cases, because the decrease may also be connected with the activity of the disease, the incidence of antinuclear antibodies or cryoglobulins and, naturally, the renal lesion observable microscopically. On the other hand Sørensen could not find any correlation between decreased C_{cr} and drug treatment (171).

The reason for elevated C_{cr} values remained unexplained in this study. However, high C_{cr} values connected with childhood nephrosis have quite often been clinically observed (100). In patients with high values of C_{cr}, proteinuria occurred in 70 per cent of the cases at the time of examination. No connection with any drug treatment, such as gold or steroid treatment, could be observed.

Material and method

Blood pressure was measured in all of the 165 patients (see page 1[illegible]) at every visit to the hospital and out-patient department. However, only the values measured in the hospital have been taken into consideration in this study. Blood pressure was measured at the hospital at least twice a week using the size of cuff corresponding to the child's size. The patient was kept in bed before the measurement. The result was not regarded as significant, until the same result was obtained on two consecutive days. The values given in Table 33, have been considered average nor-

Table 33. The mean blood pressure level in different ages in childhood

Age years	Blood pressure mmHg systolic	diastolic
≦ 4	[illegible]	60
—6	90	60
—8	90	65
9—10	100	65
11—12	1[illegible]0	[illegible]0
13—15	120	—

mal values at different ages [illegible]9. Blood pressure was regarded as significantly increased if systolic pressure was more than 2[illegible] mmHg and diastolic pressure more than 1[illegible] mmHg above the normal values for the age. Control anamnesis were the same as those described on page 29.

Results

Blood pressure was elevated in 51 children or in 30.9 per cent of the total JRA material, but was within normal limits in the control material consisting of 45 children. The difference is highly significant. The rise of systolic pressure varied from 25 to 35 mmHg and that of diastolic pressure from 15 to 25 mmHg compared with the normal values. None of the patients concerned was given antihypertensive treatment. Of the patients with increased blood pressure, 43.2 per cent were 5 years old or younger, 35.3 per cent 6—10 years, and 21.5 per cent 11—15 years at the time when high blood pressure was observed.

Frequency of increased blood pressure values — Correlation to the clinical picture of the disease

As Table 34 shows, the frequency of patients with increased blood pressure was 25.2 per cent in the group with *joint symptoms*

Table 34. *Increased blood pressure in relation to the clinical picture of the disease*

Classification of JRA	Total No. of patients	Incr. blood pressure No.	(%)
JRA with joint symptoms only	111	28	(25.[illegible])
JRA with extra-art. manifestations	54	23	([illegible].6)
Total	165	[illegible]1	(30.9)

only and in that with extra-articular manifestations the frequency was 42.6 per cent. The difference is nearly significant (p < 0.05)

— Correlation to the duration of the disease

When studying the correlation between the duration of the disease and increased blood pressure values it was observed that 55.0 per cent of these patients belonged to the group in which the duration was less than one year. In 23.5 per cent of the patients the duration was one to three years, and in 21.5 per cent over three years. In other words, in the majority of the patients, increased blood pressure was observed at an early stage of the disease, although a rise in blood pressure was also observed later on during the disease. In 14 children who had a raised blood pressure level at an early stage of the disease, the values were normalized later on as the activity of the disease decreased. Thus the frequency of persistently increased blood pressure values at the end of the observation time was 22.4 per cent

Table 35. *Increased blood pressure related to the stage of the disease*

Stage	Total No. of patients	Increased blood pressure No.	%
I + II	147	47	32.0
III + IV	18	4	22.2
Total	165	51	30.9

Table 36. *Increased blood pressure related to functional capacity*

Class	Total No. of patients	Increased blood pressure N	%
I + II	153	47	30.7
III + IV	12	4	33.3
Total	165	51	30.9

— Correlation to other clinical and laboratory findings

Stage of the disease

No significant correlation was observed between the stage of the disease and the number of hypertensive cases (Table 35). However the material is not representative enough because the groups Stage III and IV are too small.

Functional capacity of the patients

No significant correlation was found between the functional capacity and the number of hypertensive cases (Table 36). However Class III and IV are here too small.

Activity of the disease

Nearly significant correlation (p < 0.05) was observed between the frequency of hypertensive cases and the figures, ESR and Hb, describing the activity of the disease. On the other hand, no correlation was observed with positive CRP (Table 37)

Table 37. *Increased blood pressure related to the figures describing the activity of the disease*

Number	Sedimentation rate (mm/h) < 50	Sedimentation rate (mm/h) > 50	Haemoglobin (mg/100 ml) > 10	Haemoglobin (mg/100 ml) < 10	C-reactive protein positive	C-reactive protein negative
Total No. of patients	111	54	133	32	61	104
No. of hypertensive patients	25	23	36	15	19	32
Per cent	23.[illegible]	42.6	27.1	46.9	31.2	30.8

Rheumatoid factor

As Table 38 shows, no significant correlation was observed between the number of hypertensive cases and the incidence of the rheumatoid factor.

Antinuclear antibodies

In the group with antinuclear antibodies, increased blood pressure was observed in 42.2 per cent, and in that with no antinuclear antibodies in 23.8 per cent. The difference is nearly significant (Table 39).

Cryoprecipitation reaction

In the group with positive cryoprecipitation reaction, increased blood pressure occurred in 46.6 per cent and in the negative group in 27.4 per cent. The difference is nearly significant (Table 39).

— *Correlation to drug treatment*

Because 10 out of 51 patients with an increased blood pressure level (19.6 per cent) were given corticosteroids and/or ACTH, it is possible that the rise was caused by this treatment. However 58 patients altogether received corticosteroids and/or ACTH and a rise in blood pressure also developed only in 10 of these i.e. in 17.3 per cent. 38.3 per cent of the patients who did not receive this treatment had increased blood pressure values. Thus, the treatment concerned produced this effect only in some of the cases. There was no clear connection between the rise of blood pressure and the doses of corticosteroids. It was not possible to observe any correlations with other therapy forms.

Table 38 *Increased blood pressure related to rheumatoid factor*

Number	Latex positive	Latex negative	Waaler Rose positive	Waaler Rose negative
Total No. of patients	42	123	23	142
No. of hypertensive patients	14	37	8	43
Per cent	33.3	30.1	34.8	30.3

Table 39 *Increased blood pressure related to existence of antinuclear antibodies and positive cryoprecipitation reaction*

Number	Antinuclear antibodies present	Antinuclear antibodies absent	Cryoprecipitation positive	Cryoprecipitation negative
Total No. of patients	64	101	30	135
No. of hypertensive patients	27	24	14	37
Per cent	42.2	23.8	46.6	27.4

— *Correlation to serum creatinine and endogenous creatinine clearance*

Out of the total JRA cases, pathological creatinine clearance was observed in 16 children, and 12 of these (75.0 per cent) also showed increased blood pressure. In 146 children with normal creatinine clearance, increased blood pressure level occurred in 39 children i.e. in 26.7 per cent.

Serum creatinine was slightly elevated in 18 children, and 13 of these or 72.2 per cent also had an increased blood pressure level. Normal creatinine occurred in 144 patients, and 38 of them or 26.4 per cent had increased blood pressure. In other words, although the rise in blood pressure and also in serum creatinine was slight, the finding must be considered significant because the changes mainly accumulated in certain patients.

Discussion

Regularly recorded blood pressure levels in JRA patients have not been reported in previous literature. Anttila *et al.* (10) reported increased blood pressure in only 21 per cent of the 47 JRA patients with nephropathy. Only the patients requiring antihypertensive treatment had been taken into consideration in their study which re-

vealed that blood pressure does not rise until the approach of the terminal phase of the disease and most frequently it rises shortly before the uraemic phase. However it was observed in the present study that blood pressure may already have slightly risen at an early stage of the disease. The same positive correlations with the different variables (clinical picture and activity of the disease presence of ANA and Cr-glob) were observed both in patients with an increased blood pressure level and in those with pathological urinary findings or pathological results in renal function. It is therefore evident that, at least in some of the patients, increased blood pressure has a renal cause. However it is less evident that blood pressure as such would be the reason for pathological changes in the kidneys because the increase was comparatively slight. In some of the cases the rise in blood pressure was a result of corticosteroid or ACTH treatment.

Material and methods

Material

The material consisted of 57 renal biopsy and 3 autopsy specimens from 60 JRA patients altogether. After the original examination programme there was an attempt to perform renal biopsy on every third patient. However, some of the parents did not give permission for this procedure. Thus selection of the patients was not quite exact.

According to Muehrcke *et al.* (122) the specimen should contain five or more glomeruli before the biopsy specimen could be considered adequate. In this study only specimens fulfilling those criteria were included.

The age of the patients at the time of biopsy varied from 3 to 15 years. Fifteen patients were under five years, 21 patients 5—10 years, and 24 patients 10—15 years. The material consisted of 17 boys (28.3 per cent) and 43 girls (71.7 per cent). The age and sex ratios *corresponded to those of the whole series of* patients in this study.

Control material

The control material in histological renal examination consisted of 20 renal specimens taken in autopsy. The primary cause of death of these patients was a disease of the central nervous system (cerebral tumor, cerebral haemorrhage or atrophy in 14 cases), a malignant tumor in four cases, and pneumonia in two cases. The ages ranged from 2 to 17 years. Urinary infection or other kidney diseases had not been recorded in any of the cases, except proteinuria just before death in eleven cases.

Methods

— *Renal biopsy procedure*

Percutaneous renal biopsy was carried out according to the technique described by Iversen *et al.* (87) and Veraler *et al.* (186). The kidneys were localized by either urography or native X ray technique, the patient lying in a prone position. The patients were sedated by using meprobamate and pethidine chloride. The biopsy was carried out under aseptic conditions by using a Franklin-modified Vim-Silverman needle with a cutting project of 17—22 mm. The procedure was performed under local anaesthesia. After the biopsy the patients were kept in bed for two days, or until there were no erythrocytes in the urine.

— *Histological methods*

The biopsy specimens were fixed in 10 per cent neutral formaldehyde, embedded in paraffin wax, and sectioned at 3—3 μ. Serial sections were performed in some of the cases. The sections were stained by the following methods: haematoxylin-eosin, haematoxylin-van Gieson, periodic acid Schiff (PAS), Heidenhain azan-trichromic stain, Gomori's reticulin stain, silver-trichromic stain, methylviolet, and Congo red with polarizing light for amyloid (73, 144).

All the histological studies on the biopsies were performed without knowing the clinical data of the patients.

Results

Findings in juvenile rheumatoid arthritis

A survey on pathological findings in the kidneys of the patients with JRA is given in Table 40. In the following, different findings are given in detail.

— *Amyloidosis*

Amyloidosis was observed in – cases or in 3.3 per cent of the specimens. In one case amyloidosis was observed in the renal biopsy and in the other case in the autopsy specimen. Amyloidosis was observed in both cases in the walls of the small blood vessels, and in one case also in the interstitium and adventitia of the large blood vessels (Fig 2, 3) In both cases, amyloidosis was mild, and in neither case was it observed in the glomeruli

— *Glomerular changes*

Glomerular changes were observed in 17 children or in 28.3 per cent of the material. Ten patients had only glomerular changes but seven children had also tubular and/or interstitial changes.

Local glomerulitis was observable in 13 children or in 21.7 per cent of the patients (Fig. 4 5) One case was found in the autopsy and 12 in the renal biopsy specimens. In the cases concerned, an increased number of cell nuclei and accumulation of PAS positive material could be seen in the local areas of the glomeruli. The cell count of the glomeruli was otherwise normal. In the control material local glomerulitis was observed in one patient (dg. neuroblastoma) in whom proteinuria occurred shortly before death.

Only basement membrane thickening without glomerulitis was observed in four patients or in 6.7 per cent of the patients (Fig. 6) Three of these cases were observed in the biopsy and one in the autopsy specimen. In all these cases the basal membrane was only slightly thickened. The finding was best observed in PAS staining. In the control material the basement membrane was not thickened in any of the cases.

Adhesions between capillary loops and Bowman's capsule were observed in six children or in 10.0 per cent of all the renal biopsies (Fig 5) The finding was confirmed by serial sections. Local glomerulitis was also observed in five of these cases. In the

Table 40 *Structural changes in kidneys of 60 patients with JRA in relation to the clinical picture of the disease and the findings in 20 controls*

Structural changes	Number of cases with different structural changes			
	JRA with joint symptoms only	JRA with extra-articular manifestations	JRA total	Control material
Amyloidosis	—	2	2	—
Glomerular changes				
Local glomerulitis	9	4	13	1
Thickening of BM.	—	4	4	—
Adhesions	3	3	6	—
Lobulation	5	4	9	5
Glomerula sclerosis	3	3	8	5
Tubular changes				
Tubular casts	5	8	13	12
Tubular atrophy	2	6	8	—
Interstitial changes				
Infiltration				
— of round cells	—	3	3	—
— of polymorphonuclear cells	—	—	—	8
Increased interstitial tissue	4	3	7	—
Vascular changes	—	—	—	—

control material adhesions were not observed in any of the specimens.

Lobulation of glomerular corpuscles was observed in nine children. However this condition cannot be considered pathological, because the same phenomenon was observed in the control material in eight cases out of twenty However in eight cases with JRA (13.3 per cent) this phenomenon was connected with other changes six patients had local glomerulitis, two had thickened basal membranes, adhesions occurred in four cases, amyloidosis in one, and features of interstitial nephritis in two cases. Out of the eight cases in question, one was an autopsy specimen.

Some sclerosed glomeruli were observed in eight patients, and also in five patients of the control material Thus, the findings cannot as such be considered pathological. However in six patients (10 0 per cent) the finding in question was connected with other changes (Fig. 7) Three of these had local glomerulitis, three had thickening of the basal membranes, lobulation occurred in two and interstitial nephritis in four Thus, the finding may be regarded as significant in six cases, but in two cases it remained uncertain whether it was pathological or not. One of the findings was noted in the autopsy specimen, and the rest in the biopsy specimens.

— *Tubular changes*

Tubular casts were observed in 13 patients. No other changes occurred in five of them, and therefore the finding cannot as such be considered pathological. In the control material tubular casts were observable in 12 children out of 20 on the other hand, autopsy material differs from biopsy material in many ways.

Tubular casts in JRA patients were connected with other changes in eight patients (13.3 per cent) three of whom had glomerulitis. Thickening of basement membranes occurred in three cases, amyloidosis in two, tubular atrophy in seven, and interstitial nephritis in three cases. At the time of examination, proteinuria occurred in eight cases of the total group with tubular casts, and in the rest of the cases at some stage during the disease. Haematuria occurred at the time of examination in two cases, in one case it had occurred at some time before examination.

Tubular atrophy could be observed in eight children (13.3 per cent) and casts were also found in seven of these (Fig 8 9 10) Only tubular atrophy with casts was observed in two of these patients, but in the remaining six patients this was connected with other changes. Local glomerulitis was observed in two cases, thickening of basement membranes in three adhesions in two glomerular sclerosis in four amyloidosis in two, and interstitial nephritis in four In the control material, tubular atrophy was not observable although there were tubular casts.

— *Interstitial changes*

Changes in the interstitial tissue were seen in eight patients altogether (13.3 per cent) In one of the cases the specimen had been taken in autopsy and the others were biopsy specimens. Round cell infiltration in the interstitial tissue was seen in three patients, and an increase in collagenous tissue was observed in seven patients (Fig 8, 9 10) In two patients interstitial changes were observed alone, but in the others it was connected with other changes. Four patients had glomerular changes, two had amyloidosis. In four cases, tubular atrophy with PAS positive amorphous content occurred in connection with the interstitial changes. In the control material, polymorphonuclear leukocytes were observed in eight cases, but the interstitium was normal, and no round cells were to be found.

— *Vascular changes*

Pathological vascular changes were not observed with certainty in any of the patients in the JRA material. When compared with the control material, the vascular walls were

observed to be as thick, and no arteritis changes could be found.

However some increase in the connective tissue around the arterioles and small arteries was seen in two cases. In one of these patients, glomerular changes also occurred, and increased interstitial tissue in the other (Fig. 11)

Frequency of significant findings

The light microscopic picture was completely normal in 37 children. If the cases with local glomerulitis, thickening of basement membranes, tubular atrophy amyloidosis and interstitial changes are put in one group, and the cases with lobulation of glomerular corpuscle, occurrence of the sclerosed glomeruli, or tubular casts alone are considered normal, it can be stated that significant changes occurred in 23 patients out of 60 or in 38.4 per cent (Table 41) This distribution is used for mutual comparison of the findings and different clinical and laboratory variables.

— *Correlation to the clinical picture of the disease*

As Table 41 shows, significant findings were observed in 31.7 per cent of the patients with only joint symptoms and in 52.6 per cent of the patients with extra-articular manifestations also. The difference is statistically nearly significant ($p < 0.05$)

Table 41 *Frequency of significant structural changes related to clinical picture of the disease*

Number	JRA with only joint symptoms	JRA with extra articular manifestations	JRA total
No. of patients	41	19	60
No. of patients with pathological findings	13	10	23
Per cent	31.7	52.6	38.4

Patients with only lobulation, glomerular sclerosis or tubular casts were excluded from the analysis.

— *Correlation to the duration of the disease*

Histological renal changes were already observed at an early stage of the disease during the first year in 25.9 per cent of those examined. The greater the duration grew the *greater was the number of changes, being* 75.0 per cent if the disease had lasted for more than 5 years. The difference is significant (Table 42)

Table 42. *Frequency of significant structural changes related to duration of the disease*

Number	Duration of the disease		
	under 1 year	1—5 years	over 5 years
Total No. of patients	27	1	12
No. of patients with pathological findings	7	7	9
Per cent	25.9	33.3	75.0

— *Correlation to other clinical and laboratory findings*

Stage of the disease

Nearly significant correlation was observed between the stage of the disease and histological renal changes ($p < 0.05$) However most patients belonged to either Stage I or II, and this makes the assessment of the situation difficult (Table 43)

Table 43 *Frequency of significant structural changes related to stage of the disease at follow-up*

Stage	Total No. of patients	No. of patients with pathological findings	Per cent
I+II	50	17	34.0
III+IV	10	6	60.0
Total	60	23	38.4

Functional capacity

No correlation was observed between functional capacity of the patients and histological renal changes (Table 44)

Table 44. *Frequency of significant structural changes related to functional capacity of the patients at follow-up*

Class	Total No. of patients	No. of patients with pathological findings	Per cent
I+II	50	19	38.0
III+IV	10	4	40.0
Total	60	23	38.4

Activity of the disease

No significant correlation was found between the activity of the disease and histological changes. More pathological findings occurred if high ESR, low Hb values, or positive CRP were observable, but the differences were not significant (Table 45)

Rheumatoid factor

No significant correlation was observed between histological changes and the existence of rheumatoid factor (Table 46)

Antinuclear antibodies

Histological changes occurred more often in the group with positive antinuclear antibodies than in that with negative findings. However the difference is not statistically significant (Table 47)

Cryoprecipitation reaction

Histological changes occurred more often in the group with positive reaction compared to that with negative reaction (Table 47) The difference is only indicative ($p < 0.1$)

Antistreptolysin and antistaphylolysin titres

No differences in the occurrence of histological changes were observed with increased AST (> 200) and ASTA (> 2.0) values (Table 48)

Table 45 *Frequency of significant structural changes related to activity of the disease at follow-up*

Number	Sedimentation rate (mm/h) < 50	Sedimentation rate (mm/h) > 50	Haemoglobin (mg/100 ml) > 10	Haemoglobin (mg/100 ml) < 10	C-reactive protein negative	C-reactive protein positive
Total No. of patients	32	28	42	18	35	25
No. of patients with pathological findings	11	12	16	7	13	10
Per cent	34.4	42.8	38.1	38.9	37.1	40.0

Table 46 *Frequency of significant structural changes related to the existence of rheumatoid factor*

Number	Latex positive	Latex negative	Waaler Rose positive	Waaler Rose negative
Total No. of patients	20	40	8	52
No. of patients with pathological findings	8	15	3	20
Per cent	40.0	37.5	37.5	38.5

Serum gammaglobulin and alpha 2 globulin

The histological changes were more frequently found in patients with hypergammaglobulinaemia [$>$ 21.0 % of total serum protein (83)] than in patients with a normal gammaglobulin level. The difference is highly significant. Also when alpha 2-globulin was elevated [$>$ 13.5 % of total serum protein (83)] the amount of histological changes was nearly significantly higher than when alpha 2-globulin level was normal (Table 49).

— Correlation to clinical renal involvement

As Table 50 shows, only two out of 23 patients with a pathological histological findings, had no clinical signs of possible renal lesion before the biopsy. Irregular basal membrane thickening connected with lobulation was observed in biopsy in one of the cases, and distinct local glomerulitis was observed in the autopsy specimen in the other case. The other patients had proteinuria or some other signs of renal involvement. Thirty-seven patients had a normal histological

Table 47. *Frequency of significant structural changes related to existence of antinuclear antibodies and positive cryoprecipitation reaction*

Number	Antinuclear antibodies		Cryoprecipitation	
	present	absent	positive	negative
Total No. of patients	25	35	13	47
No. of patients with pathological findings	11	12	7	16
Per cent	44.0	34.3	53.8	34.1

Table 48. *Frequency of significant structural changes related to increased antistreptolysin and antistaphylolysin titres*

Number	AST		ASTA	
	normal ($\leq$ 200)	increased ($>$ 200)	normal ($\leq$ 2.0)	increased ($>$ 2.0)
Total No. of patients	45	15	43	17
No. of patients with pathological findings	17	6	16	7
Per cent	37.8	40.0	37.2	41.2

Table 49. *Frequency of significant structural changes related to increased serum alpha-2 and gammaglobulin level at follow-up*

Number	Alpha-2-globulin		Gammaglobulin	
	normal ($\leq$ 13.5 %)	increased ($>$ 13.5 %)	normal ($\leq$ 21.0 %)	increased ($>$ 21.0 %)
Total No. of patients	37	23	17	43
No. of patients with pathological findings	11	12	2	21
Per cent	29.7	52.1	11.8	48.8

finding however of these 21 patients showed clinical signs of renal involvement before the biopsy. Thus clinical signs of possible nephropathy were observed in 42 children, and 21 or 50.0 per cent of these also had histological changes.

— Correlation to drug treatment

In two cases, biopsy was performed before the commencement of drug treatment. One of the cases had previously had leukocyturia, and the other had slightly increased creatinine. However biopsy was normal in both cases. Because other patients generally received combined drug treatment, it is difficult to estimate the possible effect of drug treatment on renal changes. However when examining how many changes occurred in the different therapy groups without taking into consideration combinations of drug treatment,

Table 50. *Significant structural changes related to clinical pathological findings before the biopsy*

Structural changes	No.	Prot. +	Erythr +	Leuk. +	Inf. +	Cr incr	C_{cr} decr	PSP decr	Co decr	RB elev	No clin. findings
Amyloidosis		2	2	2	—	—	1	1	—	2	—
Local glomerulitis	13	10	3	4	3	1	3	—	—	4	1
BM thickening	4	3		1	—	—	1	1	1	3	1
Adhesions	6	6	1	1	1	—	2	—	—	3	—
Tubular atrophy	8	7	3	4	1	*	4	3	3	8	—
Interstitial changes	8	6	3	3	3	1	2	2	2	4	—
No. of patients with structural changes	23	17	8	9	5	2	5	3	4	11	2
No. of patients with normal findings	37	13	3	6	—	2	3	5	7	8	16
Whole JRA series	60	30	13	13	5	4	8	8	11	19	18

Table 51. *Significant structural changes related to different therapy groups*

Therapy	No. of patients	No. of patients with structural changes	Per cent
Antimalarial drugs	49	19	38.8
No antimalarial drugs	11	4	36.4
Gold	28	14	50.0
No gold	32	9	28.1
Corticosteroids	26	12	46.2
No corticosteroids	34	11	32.3
Salicylates	26	12	46.2
No salicylates	34	11	32.3
Phenylbutazone	39	15	38.5
No phenylbutazone	21	8	38.1
Whole JRA series	60	23	38.4

it could be observed that more changes occurred in the patients treated with gold than in the other therapy groups (Table 51) However the difference is not statistically significant.

Similarly when inspecting whether the patient had received the drug concerned or not, and examining the possible effect of drugs on this basis, it was observed that again more changes occurred in those patients who had received gold compared to those not treated with gold. The same was also observed with corticosteroids and salicylates. However the differences are not statistically significant in any of these groups. When studying the type of histological changes in different therapy groups, no significant differences are observable. However gold treatment and local glomerulitis seemed to correlated in such a way that local glomerulitis was observable in 10 cases out of 14 patients with histological changes in the gold treatment group (Table 5_)

Discussion

Amyloidosis was observed in two children or in 3.3 per cent of the cases, which corresponds to the frequency of amyloidosis in JRA material reported in the literature (10 50 62, 114, 160) In one of these cases, there were no clinical signs of renal amyloidosis. This indicates that one may well suspect that the patient has amyloidosis if the disease is otherwise severe. Both of those patients with amyloidosis received longterm corticosteroid treatment but the material is not extensive enough for determining a connection between the use of steroids and amyloidosis.

Local glomerulitis was observed in 13 children or in _1 7 per cent Th finding may as such, be considered significant because it was found in several glomeruli in the same specimen and also in serial sections. Furthermore, the finding was observed both in biopsy and autopsy specimens. This finding has not been earlier reported in JRA material although it has been observed in biopsy specimens of adult patients with RA (81 131) On the other hand, it has also been described as occuring in normal material (23, 131) and also here a similar finding was observed in one patient of the control material. However this patient had proteinuria before death.

Local glomerulitis has been most frequently observed simultaneously with other renal changes, but also alone in RA (131) In this material only this finding occurred in four patients. Proteinuria or erythrocyturia had occurred in 12 patients out of 13 before the biopsy was performed. However no clinical renal findings were observed in one of the cases. When considering the aetiology of this finding it is difficult to decide whether it is a renal lesion caused by primary disease

Table 52. *The different structural changes related to different therapy groups*

Therapy	No. of patients	Local glomerulitis	BM thick.	Adhesions	Amyloidosis	Tubular atrophy	Interst. changes
Antimalarial drugs	19	11	4	4	2	7	7
Gold	14	10	3	5	2	3	3
Corticosteroids	12	6	4	5	2	0	3
Salicylates	12	6	3	3	2	4	6
Phenylbutazone	15	8	4	4	2	5	6
No. of patients with structural changes	23	13	4	6	2	8	8

or drug treatment. The former is more likely because hypergammaglobulinaemia was observed in all the cases with local glomerulitis, and either antinuclear antibodies or a positive cryoprecipitation reaction were observed in eight cases out of 13. Thus local glomerulitis would appear as a result of an immunological process. On the other hand, it is known that gold also accumulates in the glomeruli (30 108, 185) Because local glomerulitis occurred fairly often in those who received gold treatment, there is reason to suspect that this change was caused by gold. However because the finding was also observed in three patients who had not received gold treatment, gold is not the only reason for occurrence of this finding. Furthermore, the incidence of local glomerulitis in the normal material is in contradiction to this. Local glomerulitis was more frequently observed in patients with joint symptoms only thus it is not connected with SLE or overlapping forms which are between JRA and other connective tissue disorders.

Diffuse glomerulitis, which has been described in connection with RA by many investigators in autopsy studies (14, 68 98, 157) could not be observed in the biopsy or autopsy specimens in this study

Slight thickening of basement membrane in the glomeruli was observed in four patients. Several extra-articular manifestations occurred in all these patients. However JRA diagnosis was certain, and no SLE features were observed clinically in the patients. Hypergammaglobulinaemia was observed in all these cases, and antinuclear antibodies or positive cryoprecipitation reaction in two cases. In the light of this, it might be a process caused by the primary disease. On the other hand, gold has been observed to provoke nephrotic syndrome, in which thickenings of basal membranes in the glomeruli are histologically observable (60 75 96, 108, 185) Three of the patients received gold treatment, and proteinuria developed in two of them during the treatment. Two of these patients also had amyloidosis, but amyloid could be found in the glomeruli in neither case.

Adhesions between glomerular capillary tufts and Bowman's capsule were observed in six patients. In all of them, it was connected with other glomerular findings. Six patients had local glomerulitis, and in three cases one or more sclerosed glomeruli were found. In the light of this fact local glomerulitis might be a pre-stage and lead to glomerular sclerosis through adhesions. Increased AST was found in only one patient but no violent streptococcal infection occurred in anamnesis of this patient.

Interstitial changes (increased interstitial tissue with or without round cell infiltration) were observed in 8 patients. Two of them had earlier had acute urinary infection. In addition, amyloidosis was observed in one of these patients. Thus, it is possible that the finding in these cases was caused by urinary tract infection or amyloidosis (40 84, 138, 165) The finding in six other cases may be due either to drug treatment (22 38, 39 40) or to primary disease because interstitial changes are observable in SLE and other connective tissue disorders (84 123 138) It is also known that analgesic abuse is a common reason for the occurrence of chronic non-pyelonephritic interstitial nephritis (22, 38, 39 90) Interstitial changes both in autopsy (41) and biopsy materials (31, 131) have earlier been observed in RA patients. However interstitial changes have not been seen in all earlier studies (5 139) In this material children were only given therapeutic doses of phenylbutazone and salicylates without phenacetin. Gold also accumulates in the interstitial tissue (30 108) and it is therefore possible that it could act as an irritating factor there. All of these patients received some of the above-mentioned medicines. Salicylates, phenylbutazone and gold were administered to four patients, phenylbutazone alone to two, salicylates alone to one, and gold with salicylates to one patient. Hypergammaglobulinaemia was observed in six of these patients,

antinuclear antibodies in one, and a positive cryoprecipitation reaction in two cases. Thus, this does not give any hint of possible aetiology either However remembering that the use of analgetics was controlled in all patients and that the changes concerned are also observed in other connective tissue disorders, it is possible that the primary disease may also be one of the causative agents.

Tubular atrophy was observed in eight patients. In four cases it was connected with interstitial changes. In addition, PAS-positive amorphous content in the tubuli lumen was observed in all except one. Thus it is possible that the casts resulting from proteinuria or haematuria may have caused the tubular atrophy in some of the cases proteinuria or haematuria had occurred in all the patients at some stage of the disease Amyloidosis was also observed in two patients, and this may of course be the basic reason for the above-mentioned change. Tubular atrophy has also been described in previous series of RA patients (131) Because it is known that gold accumulates in tubular cells (30 108) it could be thought that gold treatment causes this change. Gold treatment had been given to four of the patients concerned.

Increased excretion of epithelial cells in the urine during the treatment has been observed in the patients receiving salicylates (140) Four of the patients had received salicylates, and six either gold or salicylates. However no clear correlation with drug treatment is observable with certainty

Pathological vascular changes were definitely not observed in any of the patients. In contrast to previous reports (16, 34 157 163) necrotising arteritis was not observed in any of the cases. Neither could arterial or arteriosclerotic changes such as those in adult patients with RA be found (131, 139) Slightly increased connective tissue round the arterioles was found in this study in two patients, but it is not certain whether this finding is pathological. Plentiful increased connective tissue round blood vessels, similar to those described by Wilkoszewski *et al.* (195) in JRA patients, could not be observed. Vascular changes possibly caused by steroids (79 95) or changes described in ankylosing spondylitis (129) were not observed in this study



Fig. 2 Amyloid depositions in the wall of a large blood vessel. (Autopsy specimen) Kongo red staining polarized light.



Fig. 3 Amyloid accumulation in the interstitium. (Biopsy specimen) Kongo red staining, polarized light.



Fig. 4 Local glomerulitis with increased number of cell nuclei in local areas of glomerulus and accumulation of PAS positive material. (Biopsy specimen.) PAS staining

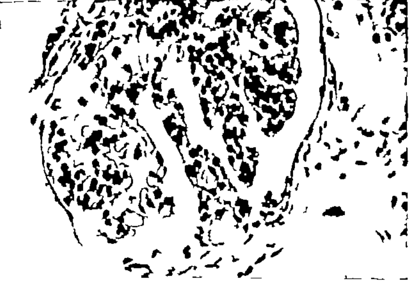


Fig. 5 Local glomerulitis with lobulation and adhesions to Bowman's capsule. (Biopsy specimen.) PAS staining



Fig. 6. Slight thickening of capillary basement membranes. (Biopsy specimen) PAS staining.



Fig. 7. A sclerosed glomerulus. (Biopsy specimen.) Gomori's reticulin staining.



F g 8. T bular cast with tubular trophy and increased interstitial tissue. (Biopsy specimen.) Van Gieson staining



Fig 9 Marked focal inflammatory infiltration with a dilated and trophic tubules. (Biopsy specimen.) Van Gieson staining.



Fig. 10. Cortical fibrosis with dilated trophic tubulus. (Biopsy specimen.) Azan staining



Fig. 11. A slight increase in collagenous tissue round the arterioles. (Biopsy specimen.) Azan staining

CONCLUDING DISCUSSION

THE INTERRELATION OF PATHOLOGICAL RENAL EXAMINATION FINDINGS

It is not possible to mutually compare the frequency of different pathological findings as such because all renal function tests and renal biopsy were not carried out on every patient. However proteinuria was the most frequent pathological finding. When the renal function tests are compared with one another it can be observed that C_{cr} was most rarely pathological and C_{O} most frequently pathological. The same phenomenon has been observed in patients with chronic pyelonephritis (91) When the clinical and histopathological renal findings were compared, there was no observable correlation. Renal function tests may be pathological and the histological picture quite normal and vice versa.

When studying the incidence of renal morphological involvement in juvenile rheumatoid arthritis, it could be observed that the frequency of histopathological findings was 38.4 per cent. This is the same figure as observed in the review of the literature when the percentage of death from renal causes in patients with juvenile rheumatoid arthritis was calculated (Table 2) The incidence of clinical involvement was somewhat greater but some of the pathological findings were temporary and therefore they were of no significance.

THE FREQUENCY OF PATHOLOGICAL FINDINGS

Correlation to clinical picture

It is known that the frequency of clinical renal involvement is very high, 60—100 per cent in other connective tissue disorders. SLE, PAN and AP (6, 15 44, 70 133, 134 138) The frequency of pathological findings in the JRA group with extra-articular manifestations was not so high but it was however higher than in the JRA patients with joint symptoms only

The renal histopathological picture is not uniform in patients with SLE PAN AP or PSS, however some common features exist (84 130, 138, 175) In other connective tissue disorders and in cryoglobulinaemia, renal lesion is believed to be caused by an immunological mechanism (37 78, 84 138) Cryoglobulins are frequently observed not only in SLE (19 78, 118) but also in RA (85, 118) and JRA (190) Thus, it is possible that cryoglobulins may play some role in the development of renal lesions in JRA. The antinuclear antibody titre is often very high in patients with SLE (110) Patients with JRA also sometimes have antinuclear antibodies (99 120) In this study the frequency was 38.8 per cent which makes an immunological mechanism plausible. The patients with extra-articular manifestations had more frequently antinuclear antibodies and positive cryopre-

cipitation reaction than the patients with joint symptoms only The difference was not significant, however It is possible that the former JRA form is one kind of overlapping form between JRA with joint symptoms only and the other connective tissue disorders.

Correlation to the duration of the disease

By inspecting all the investigation methods it was observed that some of the pathological findings were already present at an early stage of the disease The duration of the disease increased the frequency of pathological findings, mainly the incidence of proteinuria, decreased concentration capacity and histopathological changes. This increase was not so clearly observable in connection with other pathological findings.

Correlation to other clinical and laboratory findings

Stage of the disease

As the degree of severity of the disease increased (in stages III—IV) significantly more proteinuria and histological renal changes were observed. Similarly concentration capacity was most often decreased in the most severe forms of the disease but the difference was not statistically significant. Thus, the situation was completely identical when comparing the incidence of pathological findings with the duration of the disease. This is understandable for if the stage was III or IV the disease had also lasted longer in these cases. It is therefore difficult to determine whether the changes discussed above were caused by the severity or prolonged duration of the disease and consequent prolonged medical treatment

Functional capacity

Generally no significant correlation was observed between the functional capacity of the patients and the incidence of pathological findings. The frequency of proteinuria and decreased concentration capacity only had a nearly significant correlation with the functional capacity This might also in these cases be due to either the severity of the disease or to the prolonged drug therapy

Activity of the disease

A distinct correlation was observed between the figures describing activity of the disease (ESR, Hb and CRP) and different pathological results. A higher percentage of pathological findings was observed in various tests in the more active forms of the disease than in the less active forms and also during the active phase of the disease compared to the less active one in the same patients. In the histological studies the differences were not statistically significant in spite of correlation to hypergammaglobulinaemia and high α_2-globulin values. In some of the cases where the pathological findings, for instance erythrocyturia or leukocyturia, were apparently due to drug treatment, it was impossible to find a significant correlation with the activity of the disease

Rheumatoid factor

No correlation was observed between the existence of rheumatoid factor and the incidence of pathological renal findings. Significant correlation was only observed between the decreased concentration capacity and the rheumatoid factor Thus the existence of rheumatoid factor apparently does not indicate renal damage.

Antinuclear antibodies

More pathological findings were observed in various examinations when antinuclear antibodies were present than when they were absent. The difference was significant for the frequency of proteinuria and reduced concentration capacity and nearly significant for reduced creatinine clearance and increased blood pressure values. The same phenomenon

was also observed in the morphological renal changes. In that the difference was not statistically significant, however. Thus, the observation of antinuclear antibodies in JRA patients is a prognostically unfavourable sign as regards the renal damage.

Positive cryoprecipitation reaction

The existence of cryoglobulins also impairs the prognosis of the patient. The frequency of proteinuria was highly significantly greater in connection with positive than with negative cryoprecipitation reaction. Nearly significant correlation was observed in the figures for decreased concentration capacity and increased blood pressure. Histological changes also occurred more often in the group with positive cryoprecipitation than in the negative group. However the difference was only indicative.

Serum gammaglobulin and α_2-globulin

Highly significant correlation was observable between morphological renal changes and the incidence of hypergammaglobulinaemia, and nearly significant correlation with increased α_2-globulin values. The correlations with serum protein patterns were not studied in connection with other renal examinations.

Correlation to drug treatment

It is difficult to draw definite conclusions when studying the possible correlation of pathological examination findings and drug treatment. However approximately 40 per cent of the observed cases with proteinuria and erythrocyturia were apparently associated with gold therapy (Myocrisin®). Similarly PSP was reduced more often in patients who had received gold therapy than in those who had not received it. The difference was significant. Morphological renal changes were also more frequent in those treated with gold than in those not treated with gold. The difference was not significant, however.

More pathological findings were also observed in patients receiving salicylates than in those not treated with salicylates. Approximately 40 per cent of the cases with erythrocyturia were associated with salicylates or to a smaller extent with phenylbutazone intake. Renal function tests were more often pathological in patients receiving salicylates compared with those who had not received this treatment. It was not possible to observe this phenomenon with phenylbutazone although the patient groups in question were otherwise comparable with each other. Somewhat more morphological renal changes were observed in patients who had received salicylates, but the difference was not statistically significant.

Intake of corticosteroids and/or ACTH or antimalarial drugs was not with certainty observed to increase the frequency of pathological results.

One point related to drug treatment remains unexplained. All patients received nearly the same amount of different drugs calculated per kilogram of weight. Why did some patients develop complications, while the others did not? It is possible that the drug treatment only makes manifest the renal lesion caused by the primary disease.

THE PROPOSED PROGRAMME FOR RENAL EXAMINATION IN PATIENTS WITH JRA

On the grounds of the results of this study the following programme for the controlling of kidneys is suggested

1) Routine urinary examinations (protein sugar sediment, culture of bacteria) should be carried out on the patients at regular intervals of two to three months, and even more frequently if the patient receives gold treatment.
2) Renal function tests (e.g. Ce, PSP C_{cr}) should be carried out routinely on every patient at an early stage of the disease, i.e.

on initial admission to hospital Later the *controls should be carried out at least once* a year The renal concentration capacity is more likely to become pathological and PSP excretion test the next most sensitive. *A fractioned determination of PSP excretion* (urine samples 15, 30 60 and 120 minutes after the injection of phenolsulphonphtalein) would give a more reliable picture, *if it is possible to gain the co-*operation of the child. Endogenous creatinine clearance is a very suitable method of examination of glomerular function because of its simplicity

3) Measurement of blood pressure should be *one of the routine procedures.*
4) It is suggested that renal biopsy should be carried out on patients with repeated proteinuria or erythrocyturia, and on patients *with high antinuclear antibody titre* and/or positive cryoprecipitation reaction. Furthermore, renal biopsy is indicated if the disease is continuously active during *many years and rapidly progressive, and if* amyloidosis is suspected. Immunohistological examinations should be carried out, at least if antinuclear antibodies or positive *cryoprecipitation reaction are observable.*

SUMMARY

The purpose of the present study was to clarify the incidence of renal involvement in juvenile rheumatoid arthritis by using different methods. Urinary analysis, blood pressure and serum creatinine were examined longitudinally during the course of the disease. Kidney function tests were carried out at different stages of the disease, and renal biopsy was performed on every third patient in order to describe the morphological renal changes in JRA. By correlating the different pathological renal findings with clinical and laboratory findings, an attempt was made to clarify the type of JRA in which renal changes develop when they appear and what the factors are which possibly favour the development of renal lesion. In particular there was a desire to clarify what the connection is between drug treatment and observed pathological findings.

The material consisted of 165 children with juvenile rheumatoid arthritis treated at the Children's Hospital, University of Turku, in the years 1967—1970 The duration of the disease was at the end of the observation time 3 years 9 months on average, range from 1 to 14 years. The patients were divided into two groups on the basis of the existence of one or more extra-articular manifestation during the course of the disease. Joint symptoms alone occurred in 111 children and extra articular manifestations in addition in 54 children or in 32.7 per cent out of the whole series. Seventy three per cent of the patients were girls and twenty-seven per cent boys. The rheumatoid factor was positive in _5.5 per cent of the cases when it was examined by Latex fixation test and in 13.9 per cent by Waaler Rose reaction. Antinuclear anti bodies were present in 38.8 per cent and cryoprecipitation reaction positive in 18.2 per cent of the patients. Rheumatoid factor anti nuclear antibodies and cryoprecipitation reaction were more frequently positive in the JRA group with extra-articular manifesta tions than in the group with joint symptoms only However the differences were not sta tistically significant.

Section I consisted of urinary analyses, investigated at regular intervals. It could be observed that 42.5 per cent of the patients had proteinuria during the course of the disease. However in some of these patients only one period of proteinuria occurred Persistent proteinuria occurred only in 2.4 per cent, and repeated but temporary proteinuria in 25.5 per cent of the patients Erythrocyturia was observed in altogether 23.0 per cent and repeated erythrocyturia in 4.2 per cent of the total JRA group during this observation period. Significant leukocyturia was observed in 25.5 per cent, and repeated periods of leukocyturia in 6.1 per cent of the patients. The frequency of urinary infections was 11.5 per cent, that of cylindruria 4.8 per cent and that of glucosuria 2.4 per cent of the patients.

Section II consisted of the following kidney function studies determination of endogenous creatinine clearance (C_{cr}) and serum crea tinine (Cr) phenolsulphouphtalein excretion test (PSP) and determination of concentra tion and dilution capacity (Ce, De) Endogenous creatinine clearance was decreased only in 9.9 per cent out of the 162 patients exa-

mined. However C_{Cr} was permanently pathological only in 6.2 per cent of the cases, because some values normalized when the activity of the disease lessened. The results were normal in all of the patients in the control group consisting of 48 other children. Some patients in the JRA group showed extra high C_{Cr} values, over 200 ml/min/1 73 m The significance of these values remained unexplained. Serum creatinine was under 1 2 mg/100 ml in all of the patients. However slightly increased values of the mean level in different age groups were observed in 11.1 per cent of the total material. The rise was permanent only in 0.8 per cent of the cases. PSP was pathological in 19 6 per cent of the 138 patients examined. In the control material all patients showed normal values. Dilution capacity was normal in all of the patients, but concentration capacity was pathological in 31 4 per cent of 105 children. No pathological results were observed in the control material.

In Section III blood pressure level of the patients has been analysed during the course of the disease. Blood pressure was above the limit values according to the age of the child in 30 9 per cent of the patients during this observation period. However the rise of blood pressure was slight none of the patients concerned received antihypertensive treatment. In some of the patients, the blood pressure level was later normalized as the activity of the disease lessened thus the frequency of persistently increased blood pressure values at the end of the observation period was 22.4 per cent.

In Section IV the morphological renal changes in patients with JRA have been described and analysed. This material consisted of 57 renal biopsy and 3 autopsy specimens. The control material consisted of 70 renal specimens taken in autopsy from other children. The frequency of significant renal changes in JRA patients was 38 4 per cent. Amyloidosis was observed in only two children or in 3.3 per cent of the cases.

Significant glomerular changes were observed in 28.3 per cent of the patients. Local glomerulitis was observed in 21 7 per cent of the patients. This finding existed both in biopsy and autopsy specimens. Twelve out of thirteen patients with local glomerulitis and also one patient with local glomerulitis in the control material showed previous proteinuria or erythrocyturia Because local glomerulitis was observed also in one patient of the control group it is no change in the kidneys specific to JRA. Adhesions between capillary loops and Bowman s capsula were observed in 10.0 per cent of the cases. There was reason to suppose in some cases that local glomerulitis could lead to adhesions and then to glomerular sclerosis. Only slight thickening of the basement mebranes without glomerulitis was observable in four cases or in 6.7 per cent.

Tubular atrophy was observed in 13.8 per cent of the material. In four cases it was connected with interstitial changes. PAS positive amorphous content in tubuli lumen was observed in seven out of eight cases.

Interstitial changes were noted in 13.3 per cent. These changes were round cell infiltrations in the interstitial tissue and/or increased collagenous tissue.

Blood vessels seemed to be normal. However in two cases some increase in the amount of connective tissue round arterioles and small arteries was observed.

In the control material the changes discussed above were not observable in spite of one case with local glomerulitis.

When summarising the correlations of pathological results observed in different renal examinations with other clinical and laboratory findings the following conclusions could be drawn.

1. The pathological results in kidney investigations were more frequently observed in the JRA group with extra-articular manifestations than in the group with joint symptoms alone.
2. Pathological results were already observed at an early phase of the disease even before

the onset of drug treatment. It can be assumed that the findings in this group are certainly caused by the primary disease. On the other hand, according to the results given by some observation methods the frequency of pathological findings increased when the duration of the disease was longer. In these cases the reason for this may be either the primary disease or drug treatment.

3. Pathological results were more frequently observed in the patients in whom the disease was more active and more serious and who had antinuclear antibodies or positive cryoprecipitation reaction. Similarly in the histopathological section, the morphological renal changes were more frequent in the group with hypergammaglobulinaemia and increased alpha 2 globulin level. In contrast, it was not possible to find any correlations with the existence of rheumatoid factor or with functional capacity of the patients.

4. When studying the possible influence of drug treatment on the incidence of pathological findings, it was observed that gold provoked pathological urinary findings in approximately 50 per cent of the patients treated with gold. Similarly PSP was more often reduced and the frequency of histopathological findings was higher in the group treated with gold than in the group who had not received gold. Treatment with salicylates was possibly the reason for erythrocyturia in approximately 25 per cent out of the cases with haematuria. Renal function was also more often reduced in the patients who had received salicylates compared with those who had not received this treatment. Phenylbutazone caused erythrocyturia in a few cases, but it had no influence on renal function. Intake of corticosteroids and/or ACTH and antimalarial drugs was not observed with certainty to increase the frequency of pathological findings.

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CHRONIC RESPIRATORY PARALYSIS

A CLINICAL STUDY OF 12 PATIENTS IN LONG TERM RESPIRATOR TREATMENT AFTER POLIOMYELITIS

BY PENTTI HÄNNINEN HEIKKI WENDELIN
OSMO RÄSÄNEN AND MARTIN PANELIUS

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SUPPLEMENT 228 1972

From the Departments of Infectious Diseases, Pediatrics Roentgenology and Neurology University of Turku, Turku, Finland

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by

Pentti Hänninen, Heikki Wendelin Osmo Räsänen and Martin Panelius

CONTENTS

INTRODUCTION

Poliomyelitis is the most common infectious disease that can lead to respiratory paralysis. Now that various automatic apparatuses for continuous artificial respiration are available it has become possible for patients with chronic respiratory paralysis to live for years even decades. The result is that a very distinct group of patients with specific problems has arisen

There was rapid progress in the treatment of respiratory paralysis in Scandinavia during the widespread epidemic of poliomyelitis in 1952—54. The outbreak started in Denmark, where about 3000 patients with poliomyelitis were admitted to the Blegdamshospital in Copenhagen in 1952 one-third of them paralytic (37) More than 5000 cases of poliomyelitis were reported in Sweden in 1953 (16) and 633 patients with paralysis were admitted to the Hospital for infectious diseases in Stockholm (56) When the epidemic started in Finland in 1954, it was expected and the recent experience gained in the neighbouring countries could be utilized. In our country 615 cases of paralytic poliomyelitis occurred in 1954 (45) Since then the number of patients has been very much smaller and the last cases appeared during the early sixties

The most important step forwad in the care of respiratory paralysis was the institution of tracheotomy and of intermittent positive pressure ventilation (IPPV) Mainly due to the new method the mortality rate from poliomyelitic respiratory paralysis decreased in Denmark from about 80 to 38 per cent (37 43) and in Sweden from about 85 to 30 per cent (26) A contribution has also been made by other factors such as active control of the fluid and electrolyte balance and of nutritional requirements and antibiotics for the treatment of secondary bacterial infections (26) Before positive pressure respirators tank och chest (cuirass) respirators were used which do not require tracheotomy

Some studies have been made on chronic respirator patients dealing with the results after some months to some years care with positive pressure respirators (5 46) and after several years with chest or tank respirators functioning on the negative pressure principle (20 28) The results have been fairly good with both. The major difference between the two systems is seen in the mortality rate in the acute phase of the disease.

In Finland a law was passed in 1961 on the home care of patients with chronic respiratory paralysis. It made it economically possible for the patients to live at home covering the employment of nurses acquisition of respirators and other appliances and their maintainance house calls by physicians social workers and physical therapists and any drugs that might be needed. Once this law was passed, more than half of the respirator patients were transferred to home care in various parts of the country The total number in home care in Finland today is 29 Each one of them is registered with the nearest competent hospital, the staff of which is responsible for their medical care and to which the patients can be admitted if necessary

We have now taken a part of respirator patients who have been many years on home care to the Department of Infectious Diseases of Turku University to give them a thorough examination. The adaptation

to prolonged intermittent positive pressure ventilation and to extensive muscle paralysis, and the symptoms and signs of the patients were the main object of the study Sociological and psychological aspects were not included because they are under study by another team in Finland.

The long term care with IPPV is for the most part a pediatric problem at present. Neurotropic viruses which are capable of producing a chronic respiratory paralysis have easier access to the central nervous system during childhood than later in life. Therefore the present study is published in this pediatric series in spite of the fact that only about half of the patients were children at the time of contracting the illness.

CHAPTER 1

PATIENTS AND ORGANIZATION OF THE STUDY

The study group consists of twelve patients who have chronic respiratory paralysis after poliomyelitis. At the time of the study these patients had been in respirator care *for 6–15 years and the home care had lasted 2–8 years. The diagnosis of polio-myelitis was virologically confirmed in* nine patients and the other three had a typical case history and contact with virologically confirmed cases of poliomyelitis in their immediate environment at the time of contracting the illness. Some features of the disease history of the patients are listed in Table 1.

All the respirators in use were intermittent positive pressure apparatuses in which the air volume pressure and frequency can be adjusted. Every patient, in addition, had a smaller assisting respirator also operating on the positive pressure principle with compressed air as the source of energy which makes it possible for the patients to be out of doors and to make short trips and even very long ones in some instances.

Every patient was at the hospital *for five to six days Monday to Friday or Saturday*. The study procedures were performed according to a detailed prearranged scheme. The basic physical examination was made at the Department of Infectious Diseases of Turku University where the patients resided during the study period. They were also studied at the Departments of Pediatrics Roentgenology and Neurology. Additional examinations were made individually if needed. In a few patients an examination such as right heart catheterization or lumbar puncture, had to be omitted at the patient's wish.

The methods used in the study results and discussions are presented separately under five chapters.

Table 1 *Some anamnestic data on the patients*

Patient	Age	Sex	Type of Polio virus	Time in respirator care	Time in home care	Maximal time without respirator	Proneness to respiratory infections	Proneness to urinary infections	Proneness to constipation
S.L.	51 years	female	Polio 3	15 years	8 years	about 1 minute	–	++	++
R.K.	47	male	Polio 1	15	8	2–3 minutes	+	++	++
H.V.	44	male	Polio 3	13	8	nil	–	++	–
Y.R.	35	male	?	11	3	5–6 hours	–	+	+
R.P.	32	male	?	13	3	about a day	–	–	+
I.H.	39	female	Polio 3	11	7	1–2 minutes	–	–	++
K.A.	40	male	Polio 3	10	8	about 1 minute	+	++	++
T.N.	17	female	Polio 1	10	7	2–3 minutes	+	+	–
E.K.	53	male	Polio 1	9	8	10 hours	++	++	++
I.I.	23	female	Polio 1	9	6	12 hours	–	–	–
L.A.L.	31	male	Polio 1	9	5	11 hours	+	–	++
K.V.	19	female	?	6	5	some hours	+	–	–

CHAPTER 2

THE GENERAL PHYSICAL ADAPTATION

Concerning the physical adaptation to life on IPPV there are numerous aspects of importance. Some of them do not closely relate to the organ systems dealt with separately in the other chapters. Those aspects as well as the main findings of the basic physical examination are treated here.

METHODS

Conventional physical and laboratory methods of examination were used. This part of the study was performed at the Department of Infectious Diseases.

RESULTS

Basic physical findings

It can be generally stated that all the patients were active and remarkably well adapted to life in respirator care under home conditions Some features concerning the physical status are presented in Table 2

In spite of the good nutritional state in most patients the weight was surprisingly low in everyone The reason is the scarcity of the muscle mass

The measure around the chest was almost the same in inspirium and expirium in all the patients the only differences observed being 0.5–1 cm. Thus the respiratory movements are performed almost solely with the diaphragm. The mechanical resistance is smallest in the direction of paralyzed diaphragm, and the positive pressure during inspiration is not large enough to give rise to any considerable expansion of the chest.

Rales in the lungs were frequently found although the sucking of slime was always performed prior the auscultation. As the patients are not able to cough normally some extra slime is continuously present in the trachea and bronchi, even without an actual infection

With heart auscultation nothing pathological was verified in any patient and no patient had signs of heart failure But as we know how common acute myocarditis is during the acute phase of poliomyelitis (5 7 11 44 53 61) it seems possible that some of the patients may have a mild secondary cardiomyopathy In this respect reference is made to Chapter 3

The skin temperatures were generally lowered (Table 3) This has also been reported earlier (59) A weak pulse in both legs was observed in six patients very distinctly and in two patients the pulse was weak in all limbs. The superficial veins

Table 2 *Some data on the physical status of the patients*

	S.L.	B.K.	H.V.	Y.R.	R.P.	H.H.	K.A.	T.N.	E.K.	J.J.	E.M.	K.V.
Age (years)	51	4	44	25	22	29	40	17	53	13	31	19
Sex	female	male	male	male	male	female	male	female	male	female	male	female
Height (cm)	153	173	68	67	69	67	170	145	64	127	158	151
Weight (kg)	50	66	49	42	60	56	57	27	52	17	37	36
Thorax circumference (cm)												
Expirium	90.0	99.0	88.5	80.5	90.5	86.0	97.0	67.0	89.0	58.5	80.0	69
Inspirium	90.5	99.0	89.0	80.5	91.0	86.0	97.5	67.5	89.5	59.5	80.5	69.5
Pulmonary auscultation	some silent r les	some silent rales	some silent rales	normal	normal	some silent rales	moist rales	moist rales	moist rales	normal	normal	normal
RR (mmHg)	110/80	165/110	130/100	120/100	150/100	45/80	130/90	120/90	80/100	120/90	130/100	130/90
Peripheric pulses	normal	weak in all limbs	weak in all limbs	weak in lower limbs	normal	weak in all limbs	normal	weak in lower limbs	weak in lower limbs	normal	normal	normal
Abdomen	large, inert	large, inert	large, inert	normal	normal	large, inert	large, inert	normal	large	normal	normal	normal
Digital rectal examination	haemorrhoids, normal sphincter	weak sphincter	haemorrhoids, weak sphincter	normal	normal	weak sphincter	haemorrhoids	normal	normal	normal	normal	normal

Table 3 *Skin temperature (°C)*

Patient	Back of hand		Tip of 3rd finger		Upper side of foot		Tip of 3 rd toe		Below the clavicle		Inguinal fold	
	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left
S.L.	27.9	27.0	27.4	28.8	28.4	28.0	24.9	24.6	32.5	33.7	34.1	34.8
B.K.	29.0	28.1	29.4	30.1	26.3	27.1	24.5	24.1	33.8	33.3	32.9	33.9
H.V.	28.1	28.4	28.2	26.3	28.5	27.4	24.7	23.5	34.0	33.4	34.7	34.7
Y.R.	29.5	28.8	26.6	27.8	29.3	29.1	25.7	24.9	34.0	33.6	34.7	35.4
R.P.	28.4	29.5	24.8	26.0	27.6	26.6	22.3	22.4	34.2	34.5	34.1	34.2
H.H.	26.0	26.8	25.2	24.0	30.0	30.1	23.4	23.8	35.2	35.3	34.8	35.0
K.A.	31.0	29.9	29.2	27.7	31.3	30.6	27.0	26.1	35.0	35.0	34.8	36.8
T.N.	35.0	34.3	35.5	35.1	26.3	25.9	24.5	23.9	36.0	36.0	36.6	35.4
E.K.	31.1	29.7	30.8	28.9	27.6	28.8	24.9	24.5	32.9	32.7	35.5	35.5
J.L.	34.5	33.8	35.7	35.7	33.6	33.5	26.2	26.5	36.9	37.2	37.0	36.7
E.M.	31.5	34.0	31.7	33.6	28.8	28.4	26.0	25.1	36.4	36.5	35.9	36.7
K.V.	34.8	33.8	35.3	34.6	32.7	29.8	31.3	28.9	36.7	36.0	37.6	37.1

were small in most patients and sometimes very difficult to find for taking blood samples.

A large and inert abdomen with chronic constipation was found in eight patients but also the other four had paralyzed abdominal muscles as was established in the detailed neurological examination (p 24) However only two patients had a weak anal sphincter and none had a complet sphincter paralysis. Haemorrhoids were found in only three patients.

Every patient had more or less advanced kyphoscoliosis. Ankylosis in several joints was also a common finding. More detailed information on the subjects is given in Chapters 4 and 5

The occurrence of infections

Patients with respiratory paralysis are especially prone to respiratory and urinary infections (11 28 44 48) This predisposi tion is understandable and the reasons for it will be discussed (pages 10 and 29)

The susceptibility to respiratory infec tions was pronounced in six patients and it bore no correlation to the duration of respirator care (Table 1) From the slime sucked from the trachea via the tracheostomy opening a pathogenic organism was cultured in ten patients. These organisms were as follows Klebsiella aerogenes (4) Escherichia coli (3) Staphylococcus aureus (1) *Alcaligenes faecalis (1) and multiple* organisms (1) A multiple drug resistance was a common finding.

The chest X ray did not reveal changes typical of an actual infection in any of the patients. Instead four patients had radiographic changes indicative of pulmonary or pleural fibrosis probably of tuberculous aetiology

The tendency to contract urinary infections was stronger in patients who had been in respirator treatment for a longer time. The infectious organisms were rather drug resistant generally The urinary infections are presented more closely in Chapter 6

In addition two patients had minor in fections of the skin.

Concerning the influence of infections of the respiratory and urinary tracts on the functional capacity of the systems in ques

tion, on the formation of renal calculi etc., reference is made to Chapters 3 and 6

Increased levels of serum immunoglobulins were found in several patients Four of them had an elevated IgG level and one also had elevated levels of IgM and IgA. Two patients had clearly elevated serum haptoglobin levels These findings are obviously consequences of the recurrent bacterial infections. However one patient had a clearly decreased level of serum IgM. He had a highly resistant chronic urinary infection.

The AST was normal in all the patients and only one of them had a slightly elevated value of the ASTA (2.5) The erythrocyte sedimentation rate was clearly elevated in two patients (78 and 47 mm/h)

Trachea and larynx

Signs of infection were especially often found in these parts of the respiratory tract. Tracheoscopy revealed *diffuse tracheitis* in all but one of the patients. Four patients had also *granulation in the tracheal wall* close to the lower end of cannula and in two of them a *bleeding tendency* was observed at the same site. All the patients used a *silver cannula*.

By indirect laryngoscopy a diffuse flush in the *mucous membrane of the larynx* was found in seven patients particularly in the vocal cords. The functional capacity of vocal cords was maintained in all the patients and therefore no cuff was necessary on the cannula. Everyone was also able to speak.

A more detailed information on the otolaryngological findings is given separately (50)

Other observations

A hypokalaemia was generally found. The serum potassium level averaged 3 58 mEq/l range 2.8–4.5 In six patients (50 per cent) it was below 3 5 mEq/l. All the patients with hypokalaemia had used laxative regularly for long periods usually several years. Diet also plays a role in this respect. Most patients were not fond of fruit or vegetables. In two additional patients marked hypokalaemia had been diagnosed earlier and potassium therapy per os had been instituted. These two patients had no hypokalaemia at the time of the study Serum sodium was roughly within the normal limits in all the patients and so were the chlorides.

The serum iron level was generally low (average 0.062 mg/100 ml, range 0.02–0.12) and the reticulocyte count rather high (average 1 36 per cent, range 0.2–2.2) However the TIBC was not elevated (average 0.280 mg/100 ml range 0.208–0.346) The haemoglobin value was within normal limits in all the patients and so was the haematocrit. In some of the patients iron medication had been instituted.

The platelet and leucocyte counts were normal in all the patients and so were the bleeding and clotting times the prothrombin time and the partial thromboplastin time. A prolonged prothrombin time has been reported in the acute phase of poliomyelitis (33)

The hydroxyproline excretion in the urine was rather small in general (Table 4) A clearly pathologically small excre

Table 4. *Urinary excretion of hydroxyproline*

Patient	Hydroxyproline excretion	
	mg/24 hours	mg/sq.m, 24 hours
S.L.	8	5
B.K.	15	8
H.V	14	9
Y.R.	27	20
R.P	22	13
H.H.	14	8
K.A.	15	9
T.N.	17	6
E.K.	29	19
J.L.	18	23
E.M.	7	21
K.V	21	17
Average	18 9	14 0

tion was found in five patients who were very severely paralyzed incapable of managing without a respirator for more than a few minutes. The low hydroxyproline excretion obviously reflects the scanty collagen metabolism in these patients who have almost no muscle activity The possibility of hypothyreosis was excluded by determining the PBI and BEI in serum and the T_3 test, all of which gave normal results.

Some serum enzymes that were regarded as being of interest in these patients were determined. The GOT GPT and serum alkaline phosphatase were normal in all the patients. The serum CPK, the aldolase activity and the isoenzymes of LDH were slightly outside the normal limits in several patients. They are detailed in Chapter 5

To further investigate liver function, the thymol turbidity test and Hanger's test were performed and the direct and indirect serum bilirubin as well as the urinary bilirubin and urobilinogen were determined in addition to the tests mentioned before. The results were normal. Disturbance of liver function has been observed in many patients in the acute phase of poliomyelitis (3 33)

The results of the laboratory tests especially related to the cardiorespiratory skeletal neuromuscular and genitourinary systems are presented in the corresponding chapters.

DISCUSSION

In severely paralyzed patients living on IPPV for years even a decade and more the consequences cannot be predicted Pathological findings in almost any organ system would not be surprising.

In consequence of the prolonged paucity of muscle activity the peripheral circulation is weak, as peripheral pulsations and the low skin temperatures indicate and for the same reason ankylotic joints are common. Therefore regular physical therapy is essential although no improvement of muscle function can possibly be achieved. Simultaneously prevention of severe degrees of kyphoscoliosis should be aimed at although this intention also can be realized only partially

Constipation is a very understandable difficulty in patients with paralyzed abdominal muscles. If laxatives cannot be totally avoided they should be limited as much as possible. Dietary means should be emphasized. An adequate intake of potassium must be ensured even in drug form if necessary In our patient group constipation connected with a low serum potassium level and incorrect diet was a common finding. The anal sphincter is not nearly so often paralytic as the abdominal muscles and that can worsen the constipation.

Respiratory infections are among the major problems of these patients. Infectious organisms can very easily make their entry into the trachea direct through the tracheal cannula. The air is not completely freed from dust or warmed before entering the trachea. The moistening of air is not so effective as under natural conditions either The very important function of the physiological dead space is defective in tracheostomized patients. The unavoidable repeated sucking of slime if not performed adequately can also increase the risk of infections.

In the treatment of respiratory infections unnecessary use of antibiotics should be avoided, for this can lead to the emergence of multiresistant organisms. Slime in the trachea and bronchi is often regarded as an indication for antibiotic treatment. It should be noticed however that many of these patients constantly have some extra slime in the respiratory pathways and moist rales may be heard but it is not always a sign of infection. It is merely caused by irritation of the trachea and bronchi.

If the chemotherapy for respiratory infection is indicated, adaptation to the bacteriological findings is essential. Even with an adequate antibacterial treatment it is usually not possible with these patients to achieve complete freedom from pathogenic organisms in the respiratory organs (60)

The urinary infections are discussed in Chapter 6

Complications associated with the tracheal cannula can have serious consequences. Granulation close to the lower end of cannula and the bleeding tendency at the same site observed in some of our patients belong to the most common ones. These can be avoided if the form and size of the tracheal cannula are suitable for the patient, and if proper care is taken to keep it in the right position without any shift forward, backward or to any side. Continuous observation is essential, because for example the weight of the air tube can very readily change the position of the cannula. Problems attached to the tracheal cannula are more closely discussed elsewhere (50)

SUMMARY

Twelve patients with chronic respiratory paralysis after poliomyelitis were studied. The average time in respirator care was 10.9 years range 6–15 and the average time in home care 6 1 years range 2–8 All the respirators were of the IPPV type. In general the patients were remarkably well adapted to life in a respirator care under home conditions. Most of the patients had a weak peripheral circulation as indicated by the skin temperatures and peripheral pulsations. Ankylotic joints and various degrees of kyphoscoliosis were frequent findings. Constipation was a very common finding also associated with a lowered serum potassium level with regular use of strong laxatives and incorrect diet. Pathogenic infectious organisms were cultured from the tracheal slime of ten patients, and the most common organisms were Klebsiella (4) and E. coli (3) Seven patients were especially prone to urinary infections and an abundant mixed flora was found most frequently Drug resistance was a common finding in both respiratory and urinary infections. Proneness to urinary infections was more pronounced in patients who had been a longer time in respirator care but the same correlation was not found with regard to respiratory infections. A diffuse tracheitis was revealed by tracheoscopy in all but one of the patients and granulation in the tracheal wall close to the cannula was found in four patients. Urinary hydroxyproline excretion was smaller than normal in most patients. The serum iron was generally rather low

CHAPTER 3

THE CARDIORESPIRATORY SYSTEM

Of the poliomyelitis patients with respiratory paralysis 20–64 per cent have remained dependent on mechanical respiratory assistance (28 40) Many thorough cardiorespiratory studies have been made on respirator patients in the acute stage of the disease to control and to determine the effects of artificial respiration (2 9 10 18 24, 33 54 63) Various respiratory complications have occured in conjunction with the alarming initial phase of the illness in over 50 per cent of the cases but later pulmonary complications have been more rare (4) Patients convalesced from respiratory paralysis have not had any physiologically significant pulmonary defects produced by mechanical respirators or by poliomyelitis *per se* (20 40 47) In deaths from acute poliomyelitis there have often been a myocarditis (44, 53 61) or cardiovascular complications in which the prolonged insufflation pressure might have impeded the venous return causing shock (7) The cause of death in chronic poliomyelitic respirator patients has been reported to be predominantly in the respiratory system (11)

METHODS

All the examinations were made during the usual IPPV of the patient in question that is under circumstances corresponding to the patients' normal conditions. In addition, the lung volumes were measured during spontaneous respiration in cases where the patient was capable of that for some time.

The lung volumes were determined with a spirometer (Godart Pulmonet) which was connected to the respirator (Lundia) so that the sitting patient, spirometer and respirator together formed a closed system. The patient expired in the spirometer and the respirator took up the air needed for insufflation from the spirometer The same respirator was used for all the determinations. The circulating air in the respirator was measured accurately beforehand, and all leakages were eliminated. The insufflation pressure volume and frequency were adjusted to correspond to the values of the patient's own respirator The silver trachea cannulas of patients were changed into cuffed tracheal tubes to prevent air leakages from the tracheostoma.

The lung volume after passive expiration during IPPV functional residual capacity (FRC) was determined by the helium dilution technique. To measure the maximal inspiratory capacity the insufflation volume and pressure were increased as much as the patient could tolerate. The maximal expiratory capacity was also measured. The tidal volume during IPPV (V_T resp) inspiratory reserve volume (IRV) expiratory reserve volume (ERV) vital capacity (VC) residual volume (RV) and total lung capacity (TLC) were obtained from the results. If the patient could breathe spontaneously the tracheal tube was connected directly to the spirometer and the static lung volumes were measured also during spontaneous ventilation. Every determination was made at least three times and the mean of these was taken as the result. All the volumes

Table 5 *Lung volumes during IPPV*

Patient	VT resp. (l)	ERV (l)	VC (l)	VC in / of the predicted	RV (l)	RV in of the predicted	TLC (l)	TLC in / of the predicted	RV/TLC (%)	Predicted RV/TLC (%)	Minute ventilation (l/min)
B.K.	1 71	0,00	,7	34	1 35	63	3,06	45	44	30	33,3
H.V	1,1	0,00	10	3	,65	1 8	3 75	53	71	7	18,9
Y.R.	0,69	0,18	0,87	17	1 53	68	2,40	34	64	26	6
R.P	1,02	0,00	,02	9	,19	63	2,21	32	54	24	22,4
E.K.	1 30	0,27	1 57	36	2,73	118	4,30	64	64	34	3,4
E.M.	1 53	0,00	1 53	33	2,43	25	3,96	6	61	30	26,8
mean	1,22	0,08	1 30	28	1 98	93	3,28	48	60	29	22,8
J J.**	1,05	0,06	11	68	,19	124	2 30	109	52	23	15,8

* Adult
** Child

are expressed at body temperature ambient barometric pressure saturated with water (BTPS) and compared with the predicted ones (34 39)

The arterial blood sample was obtained from the radial artery and analyzed immediately The oxygen tension (P_{aO_2}) and saturation (S_{aO_2}) were measured with an oxygen electrode (Radiometer) Astrup Micro Equipment (Radiometer) was used to determine the pH, carbon dioxide tension (P_{aCO_2}) standard bicarbonate and base excess.

Electrocardiographic and vectorcardiographic examinations were made in the recumbent position. Standard 12 lead ECGs were recorded with an 8-channel electrocardiograph (Elema Mingograph 81) VCG loops and scalar xyz leads were recorded according to Frank's system (21) using Hewlet Packard VCG equipment (model 1520 A) with polaroid photography accessories. A selected collection of criteria was used in the evaluation of left and right ventricular hypertrophy (1) The normal Q—T intervals were calculated from the formula $0{,}39\sqrt{R-R}+0{,}04$ (30)

Right heart catheterization was done on five patients selected at random who consented to the examination freely No premedication was used. The x ray opaque catheter was advanced into the pulmonary artery through the prepared medial cubital vein under x ray control. The pressures in pulmonary capillary wedge (PCW) pulmonary artery (PA) right ventricle (RV) and right atrium (RA) were measured by electromanometer (Telco) placing the pressure transducer at the level of RA. The pressure tracings were recorded by 3 channel electrocardiograph (Elema Mingograph Cardirex 31 B) The oxygen saturation (S_{O_2}) of blood samples taken from the right side of the heart was measured with a Brinkman Hemoreflector MO 1 (Kipp & Zonen) Indicator dilution curves were obtained with an ear densitometer (Atlas Cardiognost R) by injecting Cardiogreen® into the right atrium. The cardiac index (CI) was estimated from the circulation times (31)

RESULTS

Lung volumes The results obtained for seven patients during IPPV are given in Table 5 Six of them could breathe for a

Table 6 *Lung volumes during spontaneous ventilation*

Patient	V_T (l)	RV (l)	ERV (l)	VC (l)	VC in % of the predicted	RV (l)	RV in % of the predicted	TLC (l)	TLC in % of the predicted	RV/TLC (%)	Predicted RV/TLC (%)	Minute ventilation (l/min)
B.K.	0,33	0,00	0,00	0,33	7	1 35	63	1,68	23	80	30	5,95
Y.R.	0 33	0,33	0 18	0,84	16	1 53	68	2,37	34	65	26	8,90
R P	0,30	0,00	0,00	0 30	6	1 19	63	1,49	21	83	24	9,60
E.K.	0,62	0,09	0,27	0,98	22	2 73	118	3 71	55	74	34	9,85
E M.	0,33	0,00	0,00	0,33	7	2,43	125	2 76	42	88	30	5,95
mean	0,38	0,08	0,09	0,56	12	1,85	87	2,41	35	77	29	8,05
J J**	0,25	0,09	0,06	0,41	25	1 19	124	1 59	75	75	23	5 50

* Adult
** Child

time without a respirator and the volumes during *spontaneous ventilation* are presented in Table 6 The results of five patients were excluded because of gas leakage during measurements.

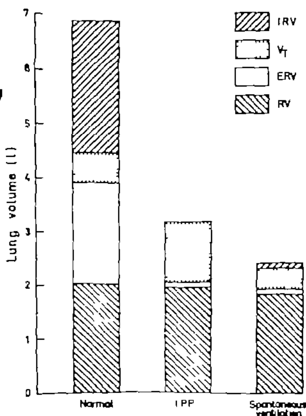


Fig. 1 Mean lung volumes in adults during IPPV and spontaneous ventilation compared with predicted normal

The insufflation volume that the patient usually used achieved the maximal inspiration in every patient; the lung volume after insufflation was the same as the total lung capacity which for the adults averaged 48 per cent of the predicted normal. In the only child examined (age 13 yrs) the TLC was the same as predicted. ERV was almost completely lacking. VC was during IPPV in adults on an average 28 per cent and in the child 68 per cent of the predicted normal. Compared with the normal tidal volume the insufflation volume was in all but one case at least double and the minute ventilation almost four times the normal, i.e. there was considerable hyperventilation. The RV was the same as predicted but the RV/TLC ratio was large in all subjects on an average double the predicted normal.

During spontaneous ventilation (Table 6) VC decreased in the adults to 12 and in the child to 25 per cent of the predicted normal. All or almost all of the VC was employed as tidal volume. The minute ventilation was normal or slightly increased. RV was the same as during IPPV but because of decreased VC the RV/TLC ratio was about three times as great as the predicted normal. The intrapulmonary mixing time of helium was quite short

Table 7 *Mean lung volumes in adults during IPPV and spontaneous ventilation in per cent of the predicted values*

Type of ventilation	VC		RV		TLC		RV TLC (%)	
	Observed (l)	Observed in of the predicted	Observed (l)	Observed in % of the predicted	Observed (l)	Observed in of the predicted	Observed	Predicted
IPPV	1,30	28	1 98	93	3,28	48	60	29
Spontaneous	0,56	1	,85	87	2,41	35	77	29

(3–4 min.) which indicates normal or almost normal distribution of the inspired gas.

The mean lung volumes in adults during IPPV and spontaneous ventilation are given in Table 7 and compared with the predicted normal values in Figure 1 The small TLC was a consequence of decreased VC while the absolute RV was as predicted. The end expiratory resting position was shifted so that breathing occurred at a more expiratory position than normally (Fig. 1)

Blood gas analysis The arterial blood gases during IPPV are presented in Table 8 Oxygen saturation was normal in all the patients. Three patients had P_{aO_2} at the lower limit of normal the others had slightly or moderately increased values. Carbon dioxide tension was lowered on an average as result of hyperventilation. In three patients the P_{aCO_2} was within normal or almost normal limits, they had the lowest P_{aO_2} values. Standard bicarbonate was on an average lower than normal and the base excess negative because of metabolic acidosis which was to some extent overcompensated, as could be seen from the pH at the upper limit of normal.

ECG and VCG findings Clinical examination revealed no signs of heart failure in any patient. Three patients had a completely normal ECG and VCG (Table 9) Right ventricular hypertrophy (RVH) was observed in four patients and left ventricular hypertrophy (LVH) in one who had a slight arterial hypertension. Pathological ST–T changes were found in four cases three of them with tachycardia. P pulmonale was found in four cases of which three had tachycardia. No patient showed signs of atrioventricular or intraventricular conduction disturbances. The duration of electrical systole in all subjects was within

Table 8 *Arterial blood gases and acid-base balance during IPPV*

Patient	P_{aO_2} (mmHg)	S_{aO_2} (%)	P_{aCO_2} (mmHg)	pH	Standard bicarbonate (mEkv/l)	Base excess
S.L.	6	98	9	7 47	8.5	—7 5
B K	04	97 3	28 5	7 41	19.5	—5 5
H V	12	98	28	7 43	20	—5
T.R	12	97 8	7	7.48	22.5	—
R.P	97	97	3	7.46	20	—5 5
K.A.	24	98 3	20	7.46	8.5	—7 5
T N	5	97.4	25 5	7.42	9.5	—6
E K	8	95	32	7.42	22	—2 5
E.M	79	94 9	35	7 36	20	—5
K.V	79	94.9	41 5	7.4	5 5	+1 5
mean		96 9	28	7.43	20 5	—4 5

7

Table 9 *Pathological electrocardiographic and vectorcardiographic signs*

Patient	Right ventricular hypertrophy	Left ventricular hypertrophy	Pathological ST T changes	Other ECG or VCG abnormalities
S.L.	—	—	+	—
B.K.	—	—	—	P pulmonale
H.V	+	—	—	—
Y.R.	—	—	—	—
R.P	+	—	—	—
H.H.	—	—	—	—
K.A.	—	—	—	—
T.N	—	—	+	P-pulmonale
E.K.	—	+	—	P-pulmonale
J.J.	+	—	+	P-pulmonale
E.M.	+	—	—	—
K.V	—	—	+	—
No of pathological cases	4	1	4	4

normal limits; the calculated mean Q–T interval was 0.34 sec. and the predicted normal 0.33 sec.

Right heart catheterization. The S_{O_2} of mixed venous blood was normal in all the patients (Table 10) The pressure in PA and the systolic pressure in RV were slightly elevated in every case. The end-diastolic pressure in RV mean pressure in RA and PCW were also slightly raised in four patients. The estimated CI was under the normal limit in one case and normal in the others.

Radiological findings. The lung on the convex side of the scoliosis was long and narrow while the contralateral lung was short and broad. The gross radiographic pulmonary pattern showed hypertranslucency reduction of the vascular markings and diminution of the lung volume Changes indicative of local emphysema or atelectasis were not detected. The radiographic pattern was fairly uniform throughout both lungs. The radiological cardiac finding was within normal limits in all the patients.

Table 10 *Mixed venous blood O_2 saturation, blood pressure in the pulmonary artery right ventricle and right atrium and cardiac index during IPPV*

Patient	Mixed venous S_{O_2} (%)	PA pressure (mmHg) systolic	diastolic	mean	wedge	RV pressure (mmHg) systolic	end-diastolic	RA pressure mean (mmHg)	Cardiac index (l/m²)
H.V	75	39	5	21	4	42	11	9	1.7
R.P	79	34	13	21	13	36	9	6	3.4
H.H.	77	32	14	22	11	35	5	2	3.0
T.N	74	38	23	26	—	42	8	7	3.4
E.K.	73	45	2	29	15	44	9	6	2.1
mean	75	38	17	24	13	40	8	6	2.7

DISCUSSION

The most characteristic alteration in lung volumes in chronic poliomyelitis respirator patients was the decreased VC which was in adults 28 per cent of the predicted normal during IPPV In all the patients the lungs were expanded maximally after the usual insufflation. The observed TLC was 48 per cent of normal and the RV/TLC ratio double the normal. An increased RV/TLC ratio has been verified in other investigations dealing with respirator treated poliomyelitis patients (20 40 47) In all these studies the absolute RV was also increased whereas in our study it was on the whole similar to the predicted normal. VC was decreased from the inspiratory part and the breathing position had shifted markedly in the expiratory direction (Figure 1) In other investigations on patients who had severe residual limitations of breathing and who still required artificial ventilation, there was no change in the resting respiratory position (20 40) In patients weaned from IPPV treatment and without deformities of the thorax and spine the resting end-expiratory position had shifted in the inspiratory direction (47) The lung volumes of our patients were quite similar to those obtained in kyphoscoliosis (8 14, 27) which also was a very general finding in our material (page 20) The long-term restriction of chest expansion and the deformities had led to very limited mobility of the thoracic cage and obviously to occluding the ventilation in some small regions of the lung (14) although no atelectatic areas could be detected radiologically The lung volumes determined gave no clear evidence of significant emphysema and ventilation was quite evenly distributed in the lungs.

The only child examined had a normal TLC during IPPV and the RV was increased relatively and absolutely

Those patients who could ventilate without a respirator for a time had the same VC during spontaneous ventilation as reported for respirator patients by other authors (20 40 47)

During IPPV the minute ventilation was about four times greater than normal. Hyperventilation has often been reported in poliomyelitis respirator patients (18 24, 47) One possible cause of hyperventilation is compensation of the hypoventilation of the occluded and atelectatic areas in the lungs (54) On the other hand the minute ventilation was almost normal during spontaneous ventilation if the patient was capable of breathing spontaneously for a time. The most likely cause of this is improvement of the ventilation to perfusion ratio and venous return when the intrathoracic positive pressure produced by respirator no longer existed (12) An increased physiological dead space in these patients can also lead to increased respiratory requirements (49) Therefore some degree of hyperventilation might be necessary for the reasons mentioned. This was very obvious in three patients (E.K. E.M., K.V) as concluded from the P_{aO_2} and P_{aCO_2} values. In the others the P_{aO_2} was slightly or moderately elevated and the P_{aCO_2} markedly lowered.

All the patients had become adapted to the high insufflation pressure and volume during IPPV and the decrease of these proved difficult. In some cases however it could be done gradually in order to avoid excessive hyperventilation.

A reduction of cardiac output in poliomyelitis has been observed during the transition from spontaneous ventilation to IPPV (9) Cardiac output has ben greatly decreased by large tidal volume in emphysematous patients but generally unchanged in patients without emphysema (29) In our study the estimated CI was normal in all but one case (H.V)

The ECG and VCG of four patients showed evidence of RVH. The pressures

Table 11 *Degree of the kyphoscoliosis and of the pulmonary radiographic change*

Patient	Age (years)	Age at onset of polio	Radiography	
			Kyphoscoliosis	Pulmonary change[b]
S.L.	51	36	mild	none
H.V	44	31	none	none
Y.R.	25	12	moderate	severe
R.P	22	12	moderate	moderate
H.H.	29	18	mild	none
K.A.	40	30	mild	severe
T.N.	17	7	severe*	severe
J.J.	13	4	mild	mild
K.V	19	13	severe*	severe

More than 90°
[b] Reduction of total pulmonary volume with emphysematous lung structure.

data for the normal Finnish population are derived from the paper of Virtama and Helelä (62)

The actual mineral content of all four bones was distinctly reduced in all the patients indicating demineralization of the entire skeleton. Visual assessment of porosis generally agreed roughly with determinations of combined cortical thickness.

An apparent tendency of the bone mineral content to decrease with the duration of respirator treatment was seen (Fig. 2) Paralysis in an extremity reduced further the mineral content of its bones and so did the increasing degree of paralysis in general (Fig. 3) Every means be it passive movements an appropriate diet or maybe fluoride or some other drug therapy should be taken to prevent the excessive demineralization and its sequalae.

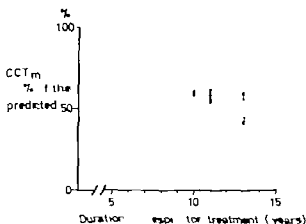


Fig. 2. The measured combined cortical thickness of the second metacarpal and metatarsal bones ($C.C.T_m$) expressed in per cent of the predicted mean value, and the duration of respirator treat

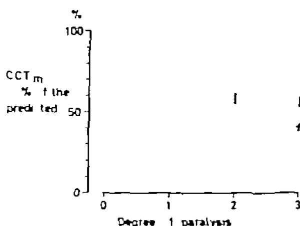


Fig. 3 The measured combined cortical thickness of the second metacarpal and metatarsal bones ($C.C.T_m$) expressed in per cent of the predicted mean value, and the degree of paralysis of the

Table 12. *Lumbar and pelvic deformities*

Patient	Lumbar scoliosis	Hypoplasia of iliac bones		Arthrosis deformans of hip joints		Arthrosis deformans of sacroiliac joints	
		Right	Left	Right	Left	Right	Left
S.L.	mild	—	—	mild	mild	severe	severe
H.V.	—	—	—	—	—	—	—
Y.R.	moderate	—		severe	—	—	—
R.P.	moderate	—	mild	—	—	—	—
H.H.	mild	—	—	severe	severe	mild	mild
K.A.	mild	—	—	mild	—	—	—
T.N.	severe	mild	severe	severe	severe	—	—
J.J.	mild	—	—	—	—	—	—
K.V.	severe	—	severe	—	—	—	—

Table 13 *Combined cortical thickness of the 2nd metacarpal bone (C.C.T.$_m$) osteoporosis and degree of paralysis*[b] *of the corresponding extremity*

Patient	Measured	C.C.T.$_m$ Normal Lower limit	Mean	Measured, in % of the normal mean	Osteoporosis	Degree of paralysis
Right						
S.L.	2.00	3.6	4.9	41	3	3
H.V.	1.25	4.3	5.5	3	3	3
Y.R.	4.00	4.	5.8	69	2	2
R.P.	2.75	3.8	5.8	47		1
H.H.	3.00	4.0	5.1	59	3	3
K.A.	3.50	4.4	5.7	6	2	2
T.N.	3.00	3.4	5.1	59	2	2
J.J.	1.50	9	4.3	35	3	1
K.V.	3.75	3.5	4.9	77	1	
Left						
S.L.	2.00	3.6	4.9	41	3	3
H.V.	50	4.3	5.5	27	3	3
Y.R.	50	4.	5.7	26	3	1
R.P.	3.50	3.8	5.9	59	1	1
H.H.	3.00	3.9	5.2	58	3	
K.A.	4.00	4.4	5.8	69	1	2
T.N.	4.50	3.3	4.9	92		
J.J.	50	2.9	4.0	37	3	2
K.V.	4.00	3.5	5.0	80		

visual estimation of osteoporosis, graded 0=none, =mild, 2=moderate and [illegible]

[b] degree of paralysis of corresponding extremities, excerpted from Chapter 5 [illegible] =moderate and 3= severe

data on Finnish population (62)



Table 14. *Combined cortical thickness of the 2nd metatarsal bone (C C T m) osteoporosis and degree of paralysis* [b] *of the corresponding extremity*

Patient	C.C.T m Measured	Normal Lower limit	Normal Mean	Measured, in % of the normal mean	Osteoporosis	Degree of paralysis
Right						
S.L.	2.00	3.4	5.1	39	3	3
H.V	2.25	3.9	5.5	41	3	3
Y.R.	3.75	3.7	5.6	67	3	1
R.P	2.50	3.4	5.7	44	3	2
H.H.	3.00	3.9	5.3	57	3	3
K.A.	3.00	4.0	5.5	55	3	3
T.N.	3.00	3.3	5.2	58	3	2
J.J.	2.75	2.9	4.6	60	1	0
K.V	3.00	3.5	5.9	51	2	1
Left						
S.L.	2.25	3.3	5.0	45	3	3
H.V	2.25	3.9	5.4	42	3	3
Y.R.	3.00	3.7	5.8	52	3	1
R.P	3.00	3.5	5.4	56	3	2
H.H.	2.70	3.8	5.3	51	3	3
K.A.	3.00	3.9	5.6	54	3	3
T.N.	3.00	3.3	5.0	60	3	2
J.J.	3.50	2.9	4.6	76	1	0
K.V	2.75	3.4	4.9	56	2	1

visual estimation of osteoporosis, graded. 0=none, 1=mild, 2=moderate and 3=severe

[b] degree of paralysis of corresponding extremities excerpted from Chapter 5 graded. 0=none 1=mild 2=moderate and 3=severe

data on Finnish population (62)

The laboratory findings reflecting the pathology of mineral metabolism are presented elsewhere (pages 9 and 29)

No correlation could be detected in this patient group between the degree of demineralization and the renal disease including calculi (see Chapter 6) Both were ...mon findings.

SUMMARY

...system of nine patients in our ...was examined radiologically ...the patients had kypho...m in a severe form. ...concomitant thoracic ...tuate the reduc...tion. Pelvic deformities were seen in seven patients. Further deformities of contracture type were detected in the hands and feet of three patients.

Combined cortical thickness was used as a modern method of assessing the bone mineral content. The entire skeleton of all the nine patients was very deficient of minerals. A decrease of bone mineral content with the increasing duration and degree of paralysis was an apparent trend. Paralysis of an extremity accentuated the reduction of its mineral content.

The patients with *urinary calculi did not* show any deviation from the general pattern of demineralization of the whole group

Fig. 2. The ... of the secon... (C.C.T.m) expr... mean value and ... ment.

CHAPTER 5

THE NEUROMUSCULAR SYSTEM

The poliomyelitis virus has a special affinity for the neurone cells of the motor system. Anterior horn cells in the spinal cord are preferentially destroyed or damaged, but the neurone cells of the premotor cortex and such brain stem structures as the hypothalamus reticular formation and cerebellar nuclei are also affected. Moreover there is evidence suggesting that subacute or chronic states of motor neurone degeneration may bear a relationship to an earlier acute anterior poliomyelitis (13) The demonstration that persistent or slow virus infections are the crucial point in the aetio-pathogenesis of several other chronic diseases of the central nervous system (22) has also been noticed.

This chapter includes an evaluation of the neurological status of our patient group. Further electroencephalographies and electromyographies enzyme determinations and basic virological studies were made for collecting more information on the possibility of cerebral affection due to poliomyelitis and for analyzing any evidence of an active progressive process in the central nervous system.

METHODS

The neurological examination included an evaluation of the degree of disability of the patients. An involvement score for different anatomical regions (35) was used (left arm right arm left leg, right leg, intercostal muscles diaphragm trunk extensors and abdominal muscles) The point scale is as follows o for no paralysis 1 for slight paralysis, 2 for moderate paralysis and 3 for severe paralysis. A test of muscle power was made according to a method and point scale described earlier (17) An approximation on the quantity of muscle volume was made by estimating the level of muscle power (the percentage of normal) in the musculature of the trunk and extremities.

Neurophysiological studies included an EEG in 10 patients EMG in 4 patients and MCV (mean conduction velocity) in only two patients because no pathological finding was to be expected with the last examination.

Antibody titres in serum against the following viruses were measured Herpes simplex, Varicellae zoster Influenza A, B C Parainfluenza 1 2 3 Adenovirus Cytomegalovirus Parotitis Measles, Poliomyelitis 1 2 3 Coxsackie A, B and ECHO (complement fixation test) and against Rubella (haemagglutination inhibition test) In addition antibodies against Poliomyelitis 1 2 3 Coxsackie A, B ECHO and Measles were measured in the cerebrospinal fluid.

The serum levels of aldolase, CPK, total LDH and LDH isoenzymes were determined as well as those of B 12 vitamin and folic acid.

RESULTS

Clinical Studies

The patients were severely disabled. Eight of them were wholly confined to bed and two could sit in a wheel-chair (one could

Table 15 *Aggregate involvement scores*

Anatomic site	Patient											
	S.L.	B.K.	H.V	Y.R.	R.P	H.H.	K.A.	T.N	E.K.	J.J	E.M.	K.V
Right arm	3 A[b]	3 A	3 A	2 A	1	3	2 A	2 A	2 A	1 A	3 A	0
Left arm	3 A	3 A	3 A	2 A	1	3	A	2	3 A	2 A	2	
Right leg	3 A	3 A	3 A		A	3 A	3 A	2 A	2	0	2 A	1
Left leg	3 A	3 A	3 A	1	2 A	3 A	3 A	2 A	2	0	2	
Intercostal muscles	3	3	3	3	3	3	3	3	3	3	3	2
Diaphgram	3	3	3	3	3	3	3	3	3	2	3	2
Trunk extensors	3	3	3	2	2	3	3	3	3	2	3	0
Abdominal muscles	3	3	3	2	2	3	3	2	2	2	2	2

Point scale 0=no paralysis
1=slight paralysis
2=moderate paralysis
3=severe paralysis

[b] A=ankylosis in one or several joints

move it himself) Two of the patients could walk independently and one of these (K.V) could climb stairs without difficulty

Involvement scores are presented in Table 15 Ankylosis in one or several joints was found in *all but one* patient (K.V) and four patients had very severe ankylotic restrictions of joint mobility in all extremities. Two of the patients (R.P and K.V) could brush their teeth and seven could use an electric typewriter including one with mouth and one with toes (B.K. and J.J) K.V was clearly the least disabled of the patients. However she was handicapped by severe scoliosis and moderate paralysis of the respiratory muscles.

The upper and lower extremities were affected in the same frequency Because this was a selected group the respiratory muscles were severely paralyzed in all the patients. The trunk extensors were severely disabled in eight patients moderately in three and not at all in one (K.V) The abdominal musculature was severely affected in five and moderately in seven patients. The paralyzed muscles were greatly atrophied in all but one patient, who had pseudohypertrophic muscles in her legs (S.L.)

Sensibility was normal for all stimuli except in one patient (K.A.) who had a decreased sense of vibration in the lower extremities. The cranial nerves were also normal in all but one patient who hade a partly paretic sternocleidomastoid muscle on the right side. Coordinative functions were normal in *all* patients as *far* as it was possible to be studied. Clinical examination revealed no signs of cerebral involvement. No fasciculations in the musculature were evident.

The muscle mass was greatly decreased in most cases. In a comparison between the muscle mass and the levels of serum aldolase and CPK some positive correlation was found, but not with serum total LDH or LDH isoenzymes (Table 16) The serum B 12 vitamin and folic acid levels were normal in all the patients Two patients had increased total protein values in the cerebrospinal fluid (125 and 184 mg/100 ml)

No antibodies against the viruses studied

Table 16. *Serum aldolase CPK and LDH with comparison to the volume of active muscle mass*

Test	Normal alue for the method used	S.L.	B.K.	H.V	Y.R.	R.P	H.H.	K.A.	T.N.	E.K.	E.M.	K.V
Aldolase	< 6 mU	4	1.2	1.8	1.4	3.0	2.3	1.4	2.5	3.5	3.3	2.3
CPK	<50 mU	19	17	2.6	31	35	5	15	16	31	24.3	17
LDH, total	110—300 Wr U	170	240	150	180	170	200	140	180	210	80	190
LDH 1 (%)	5—25	22.5	30.7	28.6	3.2	3.6	20.2	22.2	26.3	17.8	18.3	26.4
LDH (%)	30—39	4 5	38.2	40.4	38.0	30.5	38.0	40	40.4	42.6	36.5	45.5
LDH 3 (%)	23—31	26.1	19.7	25.2	27.9	29.0	25.8	16.7	22.8	28.7	27.8	19.2
LDH 4 (%)	8—14	7.2	5.8	3.5	6.2	7.9	7.4	5.2	7.0	8.9	7.9	5.4
LDH 5 (%)	3—12	2.7	5.8	2.3	4.7	9.0	8.6	5.9	3.5	0	9.5	3.6
Active muscle mass, / of normal		0	0	0	30	40	0	10	15	25	20	80

could be detected in the cerebrospinal fluid. In serum there were elevated anti body titres (1 32 or more) against Herpes simplex in four patients Cytomegalovirus in one patient and Influenza A 2 in one patient, determined in a simple serum specimen. These findings correspond to the normal incidence in healthy population.

Neurophysiological Studies

Of the 10 EEG recordings made 4 re presented normal brain electric activity and 5 showed abnormal activity with a general disturbance and a tendency to synchronized activity One of the patients (H.H.) had a definitely pathological recording, with an epileptic focus in the left temporal lobe.

Electromyography of the first dorsal interosseus muscle demonstrated either complete denervation of the muscle or a decrease of voluntarily activated muscle units. Polyphasic megapotentials were also consistent with the typical electromyographic picture of paralytic poliomyelitis. There was no suggestion of an active motor neurone disease in the EMG examination. In addition the MCW was measured in two patients although no pathological finding was to be expected, and completely normal result was gained in both.

DISCUSSION

Neurologically the clinical status was in each case typical of postpoliomyelitic paralysis. The affected muscles were atrophied and the tendon reflexes lost. The sensorium and cerebellar system were intact, and so was the cerebral integrative system (speech ability to make purposive movements, body image) Nor were there any signs of disturbance at the upper motor neurone level.

Neither clinical examination nor electromyography revealed any signs of an active "motor neurone" process. Basic virological studies did not indicate any infectious activity in the central nervous system. The serum levels of aldolase CPK and LDH were in general low and thus reflected the low muscle activity and decreased active muscle mass.

In six out of ten EEG recordings abnormal brain electric activity was observed. In one case a temporal epileptic focus had presumably developed after the poliomyelitic infection. But none of the patients had experienced any symptoms indicative of encephalitis during the acute

phase of their disease nor was there any history of anoxic periods strong enough to explain the disturbances in the brain function. On the other hand in monkeys there is experimental evidence showing that subclinical encephalitis occurs during the acute phase of poliomyelitis even in the absence of paralytic symptoms (42). The abnormalities in the EEGs could therefore be attributed to mild affection of the brain during the acute phase of the infection. The present study provides further support for the view that an associated subclinical encephalitic affection during poliomyelitis is common. The increased level of proteins in the cerebrospinal fluid in two patients indicates also a break in the blood/CSF barrier in these cases.

SUMMARY

The twelve patients with respiratory paralysis and other sequelae after poliomyelitis were examined neurologically biochemically serologically and neurophysiologically. The clinical condition was typical of the residual state after paralytic poliomyelitis. The muscle mass was greatly decreased. There were no symptoms indicating progressive motor neurone degeneration. Six out of ten patients had pathological signs in the EEG possibly due to subclinical encephalitis during the acute phase of the infection. Basic virological tests gave no indications of any persistent virus infection in the central nervous system. The levels of serum aldolase and CPK had a correlation to the muscle mass and muscle activity

CHAPTER 6

THE GENITOURINARY SYSTEM

Skeletal demineralization resulting in hypercalciuria and hyperphosphaturia with a disposition to urinary calculi formation is a common observation in paralytic or otherwise immobilized patients (15 23 51 57)

For patients with respiratory paralysis after poliomyelitis the reported incidence of urinary calculi ranges from 13 to 85 per cent for those *under* respirator treatment for a few months or longer (11 28 36 46 55) but, surprisingly few or no calculi have been found in paralytic patients after poliomyelitis without respiratory paralysis (48 52 58) The obvious explanation is the hyperventilation which elevates the urinary pH (11 46 48) However the aetiological role of bladder paralysis bladder catheterizations and urinary infections which are more frequent in patients with respiratory paralysis has also been stressed (36)

A recumbent position almost without any active movements causes some degree of urinary stasis in the posterior renal calices (48) and is another cause of both calculi formation and infection. Urinary infections also increase the disposition to urinary calculi which again predispose to infections (18 36) Thus there is a certain circulus vitiosus

METHODS

The routine urinalysis and renal function tests were performed and the urinary and serum calcium and inorganic phosphorus determined in all the patients. Roentgenograms of the kidneys and the intravenous urography were planned for all the patients but the latter had to be *omitted* in three cases because of technical difficulties

RESULTS

Urinary infections

Five patients had an actual urinary infection. Three of them had abundant mixed bacterial flora, one had Proteus mirabilis and another E. coli as the infectious organism. In addition two others had earlier had recurrent urinary infections. All these seven patients were already receiving long term chemotherapy for urinary infection when they arrived at the hospital. The infectious organisms were rather drug resistant generally In some cases it was necessary to re-evaluate the choice of chemotherapy

A disposition to recurrent urinary infections was especially pronounced in six patients. Four of the five patients who had been 13 years or longer unde or care belong to this group with the duration of respira has also been reported by oth

Radiological findings

Urinary calculi were verified tients (H.V and H.H.) A ne eft kidney was detected (H.V) who had a stagho and a distal calculus others (E.K. and Y.R. earlier for obstructiv

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A disposition to recurrent urinary infections was especially pronounced in six patients. Four of the five patients who had been 13 years or longer under respirator care belong to this group A correlation with the duration of respirator treatment has also been reported by others (55)

Radiological findings

Urinary calculi were verified in two patients (H.V and H.H.) A non-functioning left kidney was detected in one of them (H.V) who had a staghorn renal calculus and a distal calculus in the ureter Two others (E.K. and Y.R.) had been operated earlier for obstructive calculi and in a third

patient (B.K.) calculi had been found earlier in this hospital, but could not be found at the time of the study. Thus five of the 12 patients had verified urinary calculi which makes an incidence of 40 per cent.

One patient had an abnormally large urinary bladder with an inert appearance and two patients had congenital anomalies: pelvis duplex and ureter et pelvis duplex. One patient had a renal parenchymatous reduction of the right kidney, a sequel of chronic infection.

Renal function

The serum creatinine level was normal in all the patients. The average value was 1.09 mg/100 ml, range 0.9–1.3. The severe atrophy of muscle tissue however has some diminishing effect on the serum creatinine level.

The 24 hour endogenous creatinine clearance was lowered in several patients. The results are presented in Table 17. The value was decreased for every patient who had been in respirator care for 10 years or longer although two of them had no disposition to urinary infections.

The phenolsulfonphthalein test was also performed on all the patients but because the exact timing of urination is difficult

Table 17 *24 hour endogenous creatinine clearance*

Patient	Time in respirator care	Clearance/sq m
S.L.	15 years	11 ml/min
B.K.	3	6
H.V	13	25
Y.R	13	9
R.P	13	29
H.H.	1	9
K.A		9
T.N		21
E.K	9	4
J.J	9	4
E.M	9	87
K.V	6	75
Average	10.9 years	33.7 ml/min

Table 18 *The phenolsulfonphthalein test*

Patient	Time in respirator care	Phenolsulfonphthalein excretion, per cent of the amount given		
		1st hour	2nd hour	Total for two hours
S.L.	15 years	—	—	29
B.K.	13	14	30	44
H.V	3	35	15	50
Y.R.	13	33	17	50
T.N	10	29	—	—
E.M.	9	77	6	83
K.V	6	38	32	70

with these patients five tests had to be abandoned. The results for the remaining seven patients are presented in Table 18. This test also has a tendency to give worse results in patients with 10 years or longer under respirator treatment like the endogenous creatinine clearance test.

The volume of urine excreted in 24 hours was within normal limits for all the patients.

Ten of the twelve patients had a clearly decreased urinary calcium excretion and seven patients had decreased urinary excretion of inorganic phosphorus. The serum calcium level was within the normal limits in every patient, as could be expected, whereas the serum level of inorganic phosphorus was lower than normal in four patients. In one patient the urinary excretion of inorganic phosphorus was increased. The findings are presented in Table 19. The serum alkaline phosphatase was normal in all the patients.

Outside the study group all available information was collected concerning the patients with chronic respiratory paralysis after poliomyelitis who had died during the 10 years previous to the study, that is during the sixties. The number we know about is 10. Eight of them had had a renal disease (chronic pyelonephritis, uraemia, nephrocalcinosis) according to the case histories and it was also regarded as the principal or concurring cause of death in all of them. The average time of respi

Table 19. *Urinary and serum calcium and inorganic phosphorus*

	Urinary excretion (mg/24 hours)		Serum level (mg/100 ml)	
Patient	Calcium	Inorganic phosphorus	Calcium	Inorganic phosphorus
S.L.	26	160	9.3	2,7
B.K.	26	480	10,7	4,8
H.V	46	1.200	9,8	2,9
Y.R.	136	2.800	0 7	3 3
R.P.	48	490	9,0	3 9
H.H.	66	260	10,6	1 7
K.A.	62	400	9 5	6 5
T.N.	41	210	9 7	4,4
R.K.	100	590	9,8	,8
J.J.	27	590	—	—
E.M.	1	840	9 9	4,2
K.V	26	370	9,4	3,2
Average	51,2	873 3	9,85	3,49

rator treatment for these patients was 9 1 years range 5—14.

DISCUSSION

A common occurrence of urinary infections and urinary calculi was observed in this study as in many others (19 36 46 48 52 58) in patients with chronic respiratory paralysis after poliomyelitis.

Five of the 12 patients had a urinary in fection although they were all permanently under medical supervision. All these five were already receiving long term chemothe- rapy for urinary infection on arrival at the hospital. Only two patients who had earlier had urinary infections and were currently receiving chemotherapy had a normal finding in the routine urinalysis. This shows clearly the difficulty of effective treatment for urinary infections. Resistant strains are very likely to emerge during the protracted course of chemotherapy particu larly because the predisposing factors never can be totally overcome. Among these factors the most important ones are bladder paralysis lack of active movements occurrence of urinary calculi tendency to urinary stasis in the posterior renal calices the chronic constipation and maybe the lowered vitality of tissues.

Five patients had urinary calculi which makes an incidence of 40 per cent. No special method of preventing the calculi formation had been applied. However there are some means (48) that might be worth trying also in patients under respirator treatment.

The chronic constipation common in these patients makes radiological examin ation difficult. Proper evacuation of the bowel prior to examination is usually not possible and therefore for example small calculi may escape detection. This difficulty has also been pointed out by others (55)

On the basis of the observations on our patient group and the 10 post poliomyelitic respirator patients who died in Finland during the ten years previous to the study we came to the following conclusion Renal disease plays an important role in the long term prognosis of respirator patients and after 10 years under respirator treatment more or less pronounced renal failure can be expected. Chronic urinary infection and urinary calculi naturally contribute to but are not essential factors in its development.

In the acute phase of paralytic polio- myelitis hypercalciuria and hyperphosphat uria are common. After many years in a paralytic state however the situation is different. The urinary excretion of calcium and inorganic phosphorus are no longer in creased but are decreased in many patients as can be seen from Table 19 These findings are understandable. After a long period of respirator treatment the degree of skeletal demineralization is already very strong, as was also verified in the radio- logical examination (Chapt r 4) and large amounts of minerals can no longer be mo- bilized from the skeleton Diet apparently has also some influence on these findings

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Department of Infectious Diseases
University of Turku
Kunnallissairaalantie 20
20700 Turku 70
Finland

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LATE PROGNOSIS OF CHILDREN BORN INTO TUBERCULOUS HOUSEHOLDS

THE EFFECT OF ISOLATION AND SIMULTANEOUS BCG VACCINATION

BY ILKKA ANTTOLAINEN

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM

From the Department of Pediatrics, University of Oulu, Finland,
Head Professor Ole Wasz Höckert, M.D.

LATE PROGNOSIS OF CHILDREN BORN INTO TUBERCULOUS HOUSEHOLDS

The effect of isolation and simultaneous BCG-vaccination

By

ILKKA ANTTOLAINEN

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To Tuula and my daug

Contents

Introduction

The last few decades have been very auspicious in the fight against tuberculosis. Morbidity and mortality figures have declined greatly all over the world The number of children who contract tuberculosis or die from it has been particularly small in Finland during the last few years (49 50 51) The forms of tuberculosis encountered in children are also different. Tuberculous meningitis and miliary tuberculosis, which earlier assumed raging proportions, are now very rare. Prophylaxis is therefore the most important method of fighting tuberculosis in childhood and the following prophylactic principles suggested by Wasz Höckert (5, 110 111) may be taken as the guiding rules

I In order to *reduce the risk of infection*, the following points should be paid special attention for *adult* patients.

- efficacy of treatment (drugs and lung surgery)
- *visits home during hospitalization*
- chronic and recidivating cases
- asocial cases
- occurrence of resistant strains of bacteria
- detection of previously unrecorded cases in mass examinations, with special regard to risk groups.

II *Active measures* for the protection of *children*

- Isolation of infants from a tuberculous environment (institutions)
- BCG vaccination
- Chemoprophylaxis

Before the advent of BCG vaccination and modern anti tuberculous drug therapy the only way to protect infants born into tuberculous households was to isolate them. The first encouraging investigations of BCG (107) showed that BCG vaccination provided fairly good protection against primary tuberculosis for children living in a tuberculous environment. Subsequent studies indicated that the protection given by BCG vaccination even includes postprimary and secondary forms of tuberculosis, though it is not complete in such cases as Wallgren showed in his survey (108) This has also been demonstrated in our country (4 67 75 109) Chemoprophylaxis is the most recent means of protecting newborn and other children against tuberculosis.

In Finland, special prophylactic methods have been applied to children born into tuberculous households since 1936, when the Finnish Anti Tuberculous Association (Suomen Tuberkuloosin Vastustamisyhdistys) founded the first institution for the care of children born into tuberculous families. The newborn were admitted to these nurseries directly from the maternity hospital before they had been in contact with the tuberculous mother or other member of the family Since 1941 BCG vaccination has been part of this prophylactic regimen.

The incidence of tuberculosis varies greatly from one country to another which is why the prophylactic methods used and the actual treatment of tuberculosis are not identical. The purpose of the present work was to examine the results obtained by isolation in institutions in Finland

Review of the literature

GENERAL

The measures taken to protect children born into tuberculous families against infection have been manifold during the present century and a certain variation still occurs. A general survey of the published research shows that four principal methods have dominated

1) Observation in a tuberculous environment
2) Isolation of the newborn in the non-tuberculous environment of institutions or foster homes
3) BCG vaccination
4) Chemoprophylaxis

The morbidity and mortality figures for tuberculosis vary greatly even when only one method is used for there are variations in the general incidence of tuberculosis during the period under study, the length of the follow up period, and the diagnostic criteria used.

The tuberculous member of the family has been the mother in most cases the size of the series and the proportions of the different family members reported in the literature items are presented in Table 1

The severity of the disease can be seen from the mortality rates for tuberculous mothers collected from the literature and given in Table 2

In these cases the mother usually died of tuberculosis either immediately after delivery or a few months later The mortality of other family members from tuberculosis has usually not been reported

TABLE I

THE TUBERCULOUS MEMBER OF THE FAMILY (%)

	Year	No. of patients	Mother	Father	Both	Sibling	Other	Not known
Kjer Petersen et Ostenfeldt 1927 (63)	1927	245	37 9	47 1	3.4	7.8	3.8	
Jörgensen et Backer (57)	1929	1195	38.9	31.5			29 6	
Nyren (83)	1939	2962	77.0	14 0	3.0	2.0	3.0	1 0
Lorber and Menneer (68)	1959	261	26.2	20.8			53.0	
Rosenthal et al. (89)	1961	451	73.2	22.0		1.3	3.5	
Neiman et al. (79)	1967	839	51 1	23.9	14.2		10.8	

EFFECT OF MATERNAL TUBERCULOSIS ON THE FETUS

The principles for diagnosing congenital tuberculosis were first described by Beitzke in 1935 (7) and are still valid

1) verification of tuberculosis in the mother
2) verification of tuberculosis in the infant
3) exclusion of postuterine infection.

Tuberculosis of the placenta does not always lead to congenital tuberculosis (7 55) If the fetus of tuberculous mother becomes infected through the umbilical veins, the primary complexes occur in the liver or the lungs or both, while if there has been aspiration of infected amniotic fluid, the primary complex may be found in the lungs, the intestines or the middle ear Congenital tuberculosis is very rare Jentgens found about 250 case reports in the literature by 1963 (55) The present

TABLE 2.

MORTALITY OF TUBERCULOUS MOTHERS

	Year	No. of patients	Mortality (%)
Eggers et Raffo (30)	1937	207	56
Salomon (90)	1948	328	37
Ratner et al. (87)	1951	260	15
Cohen et al. (16)	1952	136	37.5
Lorber et Menneer (68)	1959	248*	15.7
Kendig (61)	1969	105	2.9

Includes the tuberculous family members covered in the study

TABLE 3.

THE RELATIVE FREQUENCIES INFANTS TUBERCULOUS MOTHERS IN THE DIFFERENT BIRTH WEIGHT GROUPS (%)

	Year	No. of patients	below 2500	2500—2999	3000—3499	3500—3999	—/over 4000
Debré et LeLong (23)	1925	433	14.0	22.0	43.0	21.0	
Guerra et Sanna (43)	1936	500	14.4	26.6			
Eggers et Raffo (30)	1937	207	35.3				
Raimondi et al. (85)	1938	1166	21.0	18.4	30.7	20.8	9.1
Urquijo et Waksmann (102)	1941	1373	20.4	18.7	31.9	20.0	9.0
Monaco (76)	1949	120	5.0	15.0	34.2	30.8	15.0
Ratner et al.** (87)	1951	260	22.0				
			64.0				
Rosenthal et al.** (89)	1961	451	4 7	19.3	52.3	17.3	6.0

The limit for prematurity was 2300 g. and the following weight group 2300—2999 g

** When the mother had mild or medium severe tuberculosis the proportion of premature infants was 22 % in cases of severe maternal tuberculosis it was 64 %.

The weight limits were 2475, 2925, 3600 and 4050 g. In 0.4 % of the cases the birth weight was not known, and 73.2 per cent were infants of tuberculous mothers.

author has subsequently found over 20 additional cases reported in the literature.

It is commonly believed that tuberculous mothers give birth to proportionate more premature infants than healthy mothers, and that the infants of tuberculous mothers have lower birth weights than other newborn. There are several studies which support this notion the results are presented in Table 3 The chronicity and the severity of the maternal disease have been postulated as reasons for the low birth weight of the infant. The most recent studies show no great differences in the birth weight compared with normal infants (89)

The frequency of prematures is understandable in the light of the chronic disease of the mother but high frequencies are naturally attributable to other reasons as well, particularly social factors.

MORBIDITY AND MORTALITY DUE TO INFECTION

This question is best elucidated by the studies in which the infants have only been observed in a tuberculous environment. Most of these reports date from the 1910s and 1920s when there was no special prophylaxis for infants born into tuberculous households, but later reports have also been published. Their data on morbidity and mortality are inadequate, however the observation periods are too short in relation to the dynamics of tuberculosis, and none of the authors have followed up the subjects past puberty

Contact with the tuberculous member of the family at home was almost continuous in all the studies, and the most frequent source of infection was the mother some of the studies are therefore restricted to discussing the prognosis of children born to tuberculous mothers.

Tuberculous meningitis was the most common cause of death.

The morbidity and mortality risk due to infection is illustrated by the findings presented in Table 4

PROPHYLACTIC METHODS

Isolation from the tuberculous home

The principles of this prophylactic method were first described by Grancher in France as early as the beginning of the

TABLE 4.

MORBIDITY AND MORTALITY RATES DUE TO INFECTION.

	Year	Country	No. of patients	Period	Observation time	Morbidity ( )	Mortality ( )
Bernard et al. (8	1925	France	66	prior to 1925	4 yrs		81.8
Kjer Petersen et Ostenfeldt 63	1927	Denmark	245	1919—19.5	first year of life		6.1
Deutsch-Lederer 27	1929	Germany	196	prior t 1928	first year of life	71 4	6.6
Graham (40	1929	India	360	1916—1927	1—12 yrs	19 0	
Jorgensen et Backer 57	1929	Norway	1195	1911—1925	1—15 yrs		8.0
Zuman (119	1932	Italy	30	prior to 1932	1—11 yrs		13.3
Della Porta (76	1960	Italy	.0	prior to 1960	1—12 yrs	30.0	
Durando et Bertoli 29	1960	Italy	63	19.0—19.8	1—9 yrs	27 0	
Wasz-Höckert et Salmi (110	1964	Finland	131	1935—1944	first year of life		35.0

century (21). According to him, however, isolation did not take place immediately after birth but during the first few years of life, which means that the risk of infection greatly reduced the value of isolation. In the early 1920s, the French adopted the practice of isolating the newborn immediately after birth, and this method of prophylactic isolation was then introduced in several countries. But there has still been great variation in the time and duration of isolation of the infant, which is reflected in the varying morbidity and mortality figures reported in the studies.

The National Lung and Heart Association of Sweden (Svenska Nationalföreningen mot Lung och Hjärtsjukdomar) launched a program for protecting children born into tuberculous families against infection as early as 1915. The newborn were first isolated in foster homes, later in institutions, for about two years or longer depending on the risk of exposure at home. This method continued in use until 1937, when the series obtained by then were analyzed (83). The follow up periods ranged from one to 23 yers. Medin in 1926 (74) and Nyren in 1929 (82) published interim reports on parts of this study. The total series consisted of 3 297 children isolated at different points of time, of whom 2 962 underwent a follow up examination. The morbidity and mortality from tuberculosis in relation to the time of isolation are given in Table 5.

TABLE 5.

THE EFFECT O THE TIME ISOLATION ON MORBIDITY AND MOR ALITY FROM TUBERCULOSIS

1. *Nyren (83)*

	No. of patients	%	Died	%	Contracted tuberculosis	%	Total	%
Isolated during the 1st day	272	9.2	3	1.1	8	2.9	11	4.0
Isolated during the 1st month	717	24.2	18	2.5	26	3.6	44	6.1
Isolated during the 2nd—3rd month	404	13.7	26	6.4	21	5.2	47	11.6
Isolated during the 4th—6th month	424	14.3	29	6.8	19	4.5	48	11.3
Isolated during the 7th—12th month	593	20.0	22	3.7	50	8.4	72	12.1
Isolated during the 2nd year of life	552	18.6	22	4.0	51	9.2	73	13.2
	2 962	100.0	120	4.1	175	5.9	295	10.0

2. *Bernard et al. (8)*

	No. of patients	Died of tuberculosis	%	Contracted tuberculosis	%	No tuberculosis	%
Isolated immediately after birth	265	—		—		265	100
Exposed, isolated	171	13	7.6	4	2.3	154	90.1
Not isolated	66	54	81.8	—		12	18.2

TABLE 6.

MORTALITY AND MORBIDITY RATES OF CHILDREN ISOLATED AS NEWBORNS FROM TUBERCULOUS HOMES

	Year	Country	No. of patients	Period of study	Period of isolation	Follow-up period	Morbidity (%)	Mortality (%)
Guerra et Sanna (43)	1936	Italy	500	1930—1934	4 weeks—	—5 yrs	1 6	0.8
Eggers et Raffo (30)	1937	Chile	207	Prior to 1937	15 days— 1 year	—5 yrs	16.0* 47.0*	
Monaco (76)	1943	Italy	120	Prior t 1943	1 yr	1 yr	0	0
Salomon (90)	1948	Chile	334	1943—1947	1 yr—	1—5 yrs		0.9
Budetta et Benevent (11)	1962	Italy	120	1952—1961	3 yrs	1—10 yrs	3.0	1 7
Kendig (61)	1969	USA	75	1948—1967	6 weeks—	1—20 yrs	50.7	2.7

Isolated immediately after birth
Isolated later

Nyren s results clearly show that the earlier the infant was isolated from ex posure, the better its chances of avoiding infection.

The observation period used by Bernard et al was four years, and the children who were isolated immediately after birth remained in the institution all that time. (Table 5)

The mortality and morbidity figures obtained in other studies of isolation of the newborn are presented in Table 6

During the period of isolation the child is fully protected from exposure to tuber culosis (8 76) but the risk of infection exists even when the source of contagion has been found inactive, as has been shown by Kendig (61) In his study 16 of the 38 mothers whose children con tracted tuberculosis were found to be non-infectious (sputum and x ray findings negative)

In Finland Pipping maintained in 1916 that the only reliable method of protecting children from tuberculosis was to isolate them (95) In 1932, the Finnish Anti-Tuberculous Association (Suomen Tuber kuloosin Vastustamisyhdistys) appointed a committee including Arvo Ylppö as the pediatrician representative, to design a plan for the protection of the healthy newborn of tuberculous families against infection. On July 1 1936 the first institution specially designed for this purpose* was opened for infants born to tuberculous mothers. At first, the children were isolated for an average of two years, but since 1941 when BCG vaccination was included as part of this prophylactic program, the period of isolation has been shortened considerably

BCG vaccination

Judging from the number of investi gations published BCG vaccination has been the most interesting aspect in the attempts to protect the healthy newborn of tuberculous families against infection.

The report of Wallgren, who observed 230 BCG vaccinated children, is a classic study of the protective effect of BCG vaccination on children living in a tuberculous environment (107) The subjects were exposed to tuberculosis for periods ranging from two to 72 months

These institutions have been partly maintained by the revenue from pecial Christmas stamps.

and only one of them (0 4 per cent) developed tuberculosis by the end of the follow up period

Rosenthal et al carried out a well controlled investigation of the protective effect of BCG vaccination on children born into tuberculous families (89) Their series included 231 children of tuberculous families who were isolated and BCG-vaccinated after birth If the mother had active tuberculosis, BCG vaccination was preceded by a tuberculin test and radiological examination, to exclude cases of congenital tuberculosis. The control group comprised 220 children of tuberculous families who received physiological saline solution as placebo The two groups were identical in race, sex, area of birth, weight, follow up period and general condition. The average period of isolation was 10.2 weeks in both groups. Isolation was discontinued when there was no further risk of infection at home, and when the tuberculin tests of the subjects in the study group had become positive The observation periods varied ad 13 years. Only three of the BCG-vaccinated subjects (1 3 per cent) contracted tuberculosis, and none died. In the control group, four children (1.8 per cent) died and 11 (5 0 per cent) contracted tuberculosis, which brings the total morbidity of the control group to 6.8 per cent The morbidity rate from tuberculosis was thus fivefold higher in the non vaccinated group.

Kendig observed 30 BCG-vaccinated children of tuberculous mothers for an average of eight years none of children contracted tuberculosis (61) Jentgens had the same experience with 100 infants of tuberculous mothers, despite the fact that four infants returned home while still tuberculin-negative, and seven continued to be exposed to tuberculosis at home However the follow-up period was short, only 1—2 years (56) Wasz Höckert and Salmi conducted follow-up examinations of 127 children born during 1940—1960 who had been isolated and BCG-vaccinated immediately after birth. The periods of isolation ranged from two to 24 months and none of the subjects had developed tuberculosis by 1962 (110)

The data on the study group and the control group are inadequate in other studies, and the tuberculosis mortality and morbidity figures differ greatly Kereszturi et al. (62) Neimann et al. (79) and Lorber and Menneer (68) returned the BCG-vaccinated infants to tuberculous homes. According to Kereszturi et al., the mortality rate after the first year of life was 1.8 per cent against 9 7 per cent for the control group, which was not BCG-vaccinated (62) In the BCG-vaccinated group of Neimann et al. which consisted of 859 children, 1 0 per cent contracted tuberculosis during the 10-year follow up, while 1.8 per cent of the control group (326 children) died of tuberculosis and altogether 66.9 per cent contracted the disease (79) The series of Lorber and Menneer included also older infants and the BCG-vaccinated were kept isolated until they became tuberculin-positive. By the end of the follow-up period of 5—8 years, 1.2 per cent had tuberculosis (68)

The highest morbidity figures for BCG-vaccinated infants of tuberculous families were reported by Krzyszkowska and Romanowska (64) and Graffar and Anel (39) In the former investigation the BCG vaccination group comprised 204 infants, 75 per cent of whom were vaccinated before the mother was diagnosed as tuberculous a total of 5.8 per cent contracted tuberculosis during the follow-up period of 20 years. Their control group consisted of 176 children, 31.8 per cent of whom contracted tuberculosis. Twentyone per cent of the mothers in the study group and 31 per cent of the controls had persistent active tuberculosis (64) The series of Graffar and Anel consisted of 86 children of tuberculous families the infants were BCG-vaccinated immediately after birth or a little later None of those vaccinated died of tuberculosis, though 10.5 per cent became infected The control group comprised 80 children two died of tuberculous meningitis and 48.8 per cent contracted tuberculosis. The two groups were comparable in socio-economic background and risk of exposure (39)

The figures reported for tuberculosis

morbidity in the above mentioned studies differ considerably. The obvious reason for this is the variation in the general incidence of tuberculosis during the study period, the risk of exposure at home and the length of the follow up period. Accordingly, the series are not mutually comparable, but they do provide a rough idea of the prognosis of a child born into a tuberculous family when the child has received the protection of BCG vaccination.

Chemoprophylaxis

The chemoprophylactic method of preventing tuberculosis acquired practical significance when an effective, safe and inexpensive drug became available. Isoniazid, which was introduced as a chemotherapeutic agent in 1952, proved to have these properties. After 1954 several reports were published from all over the world demonstrating that isoniazid could be used for prophylactic purposes as well as for the actual treatment of tuberculosis (e.g. 24, 66).

The term chemoprophylaxis is used in several contexts in the literature. One proposed division is into primary chemoprophylaxis, which would refer to the prevention of infection, and secondary chemoprophylaxis, which implies retardation of the development of the existing infection. Chemoprophylaxis can also be divided into *early* chemoprophylaxis, which is initiated even before any verified infection, and *actual* chemoprophylaxis, which is INH medication given to children living in a tuberculous environment to prevent infection. In cases where infection has already taken place it seems reasonable to talk about chemotherapy, which would be early in symptomfree cases, and actual chemotherapy in cases where sym

TABLE 7

MORBIDITY RATE FROM TUBERCULOSIS IN CHEMOPROPHYLACTIC INVESTIGATIONS DURING THE YEAR OF THERAPY AND THE SUBSEQUENT FOLLOW-UP PERIOD.

			Subjects who contracted tuberculosis/ 1 000 subjects investigated					
	No. of patients		During therapy		After therapy		Change (%)	
	Placebo	INH	Placebo	INH	Placebo	INH	During	After
Mount et Ferebee 1961 (77)	1306	1354	22.9	1.4	7.4	2.2	—93.8	—70.3
Ferebee et Mount 1962 (36)	13945	13902	6.2	1.4	16.1	8.6	—77.4	—46.6
Ferebee et al. 1963 (37)	12326	12884	1.7	0.2	7.4	3.4	—88.2	—54.1
Nyboe et al. 1963 (81)	8141	7769	3.1	2.3	—	—	—25.8	—
Bush et al. 1965 (12)	1096	1142	10.0	7.0	—	—	—30.0	—
Del Castillo et al. 1965 (14)	194	133	30.9	22.6	124.0	134.0	—26.9	+8.1
Egsmose et al. 1965 (31)	376	399	74.5	15.0	10.6	7.5	—79.9	—29.2
Horwitz et al. 1966 (46)	3907	4174	18.7	12.7	64.0	44.3	—32.1	—30.8
Comstock et al. 1967 (20)	3017	3047	15.2	5.3	30.8	13.8	—65.1	—55.2
Curry 1967 (22)	1192	2910	—	—	20.9	0.34	—	—98.4
Veening 1968 (101)	178	133	70.3	7.5	23.4	0.0	—89.3	—100.0

ptoms have already appeared. According to Ferebee, chemoprophylaxis refers to the prevention of infection (35)

The recent recommendations for a wider use of isoniazid (INH) as a prophylactic agent are based on comprehensive studies of a general population or school children and students. Ferebee has written an excellent review of these studies (35) part of which is tabulated here (Table 7)

The efficacy of the protection given by isoniazid varies from the statistically not significant differences in the less extensive studies to the highly significant differences recorded in larger materials. This great variation in morbidity rates reflects real differences in the risk of exposure as well as differences in the diagnostic criteria and the inclusiveness of the follow up. The difference between the group receiving placebo and that treated with isoniazid is practically constant even after the termination of treatment, which means that isoniazid therapy also has a persisting effect. In the studies which show the effect of isoniazid to be small or non existent the series were probably given inadequate medication (35)

Isoniazid has proved to be a drug with few side-effects (44 69 84) Ferebee and Mount reported side-effects in 1.9 per cent of the subjects in the isoniazid group and 1.5 per cent of those receiving placebo. Side effects were more common in the older age groups. Thirty five per cent of the side-effects were gastrointestinal, 26 per cent allergic, 27 per cent neurological, and 12 per cent others (weight gain, fatigue, dyspnea, chest pain) The side-effects generally appeared during the first month of treatment later the incidence of side-effects was the same in the isoniazid and placebo groups (36) Recently complications to INH prophylaxis from the liver have been discussed by Ferebee (53)

Very few studies have been published on the protective effect of chemoprophylaxis on children of tuberculous families. In the *chemoprophylaxis of the newborn* special attention should be paid to the possible immediate or subsequent toxicity of the agent. The abnormal reactions of infants to various pharmacological agents underline the necessity for great care and accuracy in the diagnosis of the disease and the dosage of the drug. Isoniazid is the only drug used so far in the chemoprophylaxis of tuberculosis. It has been suggested that isoniazid administered during the neonatal period might accumulate and thereby lead to severe unexpected reactions, because its metabolic pathway is the same as that of sulfa the excretion rate of which during the neonatal period does not reach the adult level (17 116) According to Vest and Rossier however the acetylation activity of the newborn is at adult level, which makes it possible to treat a newborn infant with isoniazid without any great risk (105) Mason and Russel (72) applied in practice the method of determining the acetylator phenotype described earlier (54) and their results show that it is possible, with minimal disturbance of routine, to determine the acetylator phenotype of most patients who take INH regularly. This information is useful clinically in that it aids the choice of a rational dosage regimen for INH that would minimize the side-effects, helps avoid therapeutic incompatibilities, such as phenytoin intoxication, and identifies the patients for whom pyridoxine supplements may be required.

The effect of INH prophylaxis on the newborn and infants of tuberculous mothers was well demonstrated by Dormer et al. (28) Of the 98 mothers they examined, 49 had positive sputum. Each newborn was kept in a cot next to its mother's bed and the mother was allowed to handle her infant freely. Up to the age of six months the infants were given 25 mg of isoniazid twice daily and thereafter 50 mg twice daily. The investigation was carried out over the period 1956—1958, during which time none of the 94 children who received isoniazid regularly contracted tuberculosis. Four of the 98 became tuberculin-positive, but in all these cases medication had been interrupted temporarily. Medication was continued at home when necessary. There was no actual follow up, but even then this study demonstrated the effect of INH in preventing primary infection. In our country this question has been studied by Wass

Höckert and Salmi (115) Their investigation covered 190 newborn and infants who had been exposed to tuberculosis The follow up period of INH chemoprophylaxis (5—10 mg/kg body weight/day administered for 3—12 months) was four years, after which seven subjects (3 7 per cent) were found to have contracted primary tuberculosis.

It is understandable that ethical reasons have prevented investigations of placebo versus INH in the newborn.

Purpose of the study

The purpose of the present investigation was to ascertain the effect of isolation and simultaneous BCG vaccination on children born into tuberculous families as regards

— their mortality from tuberculosis,
— their morbidity from tuberculosis,
— their mortality during isolation

and, in the groups of children who contracted tuberculosis or died from it, to find the reasons which led to *the infection*. The correlation between maternal tuberculosis and the infant's birth weight was investigated

However the important question of the maternal deprivation caused by isolation has not been studied.

Subjects and methods

The subjects of the present study were born into tuberculous households during the years 1945—1964 They were isolated in special institutions immediately after birth *before* they had any contact with the tuberculous mother or other member of the family BCG vaccination was performed during the first few weeks. When the tuberculin test had become positive, at the age of about two months, the infants were allowed to return home, provided there was no longer any risk of infection Frequently however particularly during the first few years of the study period the mother was unable to assume *responsibility for her infant after the two* months owing to inadequate nursing facilities, and most children had to be kept in these nurseries longer than would have been necessary for medical reasons.

INSTITUTIONS

Three special nurseries for the care of infants born into tuberculous families have been maintained by the Finnish Anti Tuberculous Association In addition the Pitäjänmäki Children's Home maintained by the Deaconess Institute of *Helsinki looks after children born into* tuberculous households in Helsinki These children were not included in the present study since a report on them has already been published earlier (110) The institutions established specially for the care of infants born into tuber culous families are

— The nursery at Tampere, open since 1936
— The nursery at Oulu, 1945—1969
— The nursery at Kuopio, 1954—1964

At present only the one institution at Tampere is in operation

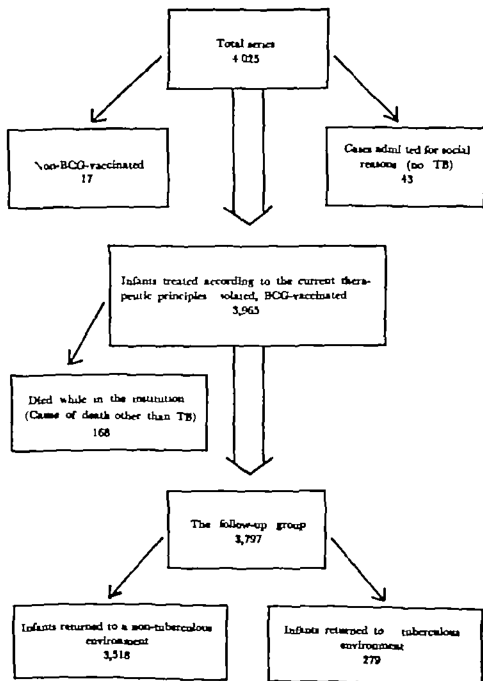
The need for beds has decreased during the last 10 years as the general incidence of tuberculosis has declined. Earlier particularly in the late 1940s and early 1950s, it was sometimes even necessary to return infants to tuberculous homes

TABLE 8.

NUMBER OF INFANTS TREATED DURING 1945—1964 IN THE INSTITUTION FOR THE CARE O INFANTS BORN INTO TUBERCULOUS FAMILIES, LISTED PER YEAR AND INSTITUTION, AND THEIR SEX DISTRIBUTION

	Tampere		Oulu		Kuopio		Total
	Boys	Girls	Boys	Girls	Boys	Girls	
1945	41	40	4	9			94
1946	45	52	21	27			145
1947	58	49	33	26			166
1948	41	43	41	28			153
1949	42	50	29	38			159
1950	49	38	42	43			172
1951	40	29	47	48			161
1952	45	46	46	43			180
1953	37	43	37	53			170
1954	49	37	36	55	33	38	248
1955	43	44	41	44	41	42	255
1956	40	45	48	47	41	39	260
1957	46	39	34	37	36	24	216
1958	43	35	43	48	27	37	233
1959	47	40	45	35	35	28	239
1960	47	32	45	46	25	38	233
1961	52	32	63	47	36	31	261
1962	47	40	63	41	37	37	265
1963	31	40	52	34	34	31	222
1964	47	35	45	33	14	18	190
	800	809	822	782	359	363	4,025

Figure 1 Distribution of the series into groups



because of the shortage of nursery beds. These children are also included in the present series.

The years 1945—1964 were chosen for the study because the methods of treatment in the different institutions were comparable during that time and thus a sufficiently large series could be collected.

SUBJECTS

Altogether 4 025 *newborn* were treated in the three institutions during the period 1945—1964 as can be seen from Table 8 and Figure 2. The distribution of the total series into groups is presented in Figure 1.

The socio-economic background of the families under study was ascertained from the parents' profession and the number of healthy and tuberculous elder children in the family. The families were classified according to occupational standing (86). In 7.9 per cent of the cases the profession of neither parent was mentioned in the patient register, case record or follow-up card. Seventy seven per cent of the children were born into families which belonged to the social groups III—V as can be seen from Table 9.

The numbers of elder children and tuberculous children in the tuberculous families investigated are shown in Tables 10 and 11.

TABLE 9.

SOCIAL GROUPS OF THE TUBERCULOUS FAMILIES INVESTIGATED.

	I	II	III	IV	V	Not known	Total
Oulu	31	149	195	647	336	231	1,589
Tampere	50	278	367	669	258	64	1 686
Kuopio	14	92	119	268	178	19	690
	95	519	618	1,584	772	314	3,965
	2.4	13.1	17.2	39.9	19.5	7.9	100.0 %

I = Managerial position, etc.
II = self-employed, supervisors, senior office staff, etc.
III = skilled workers, junior office staff etc.
IV = auxiliary workers, manual labourers, etc.
V = farmers

TABLE 10.

THE FREQUENCIES OF FAMILIES ACCORDING TO THE NUMBER OF ELDER CHILDREN

	Number of families	%
No elder children	933	23.5
1 older child	727	18.4
2 elder children	666	16.8
3 elder children	497	12.5
4 elder children	382	9.6
5 elder children	241	6.1
≥ 6 elder children	483	12.[illegible]
Not known	36	0.9
	3,965	100.0

TABLE 11.

OCCURRENCE OF TUBERCULOSIS IN THE ELDER CHILDREN OF THE FAMILY

	Number of families	
No elder children with tuberculosis	3,372	85.0
1 older child with tuberculosis	384	9.7
2 elder children with tuberculosis	119	3.0
≥ 3 elder children with tuberculosis	54	1.4
Not known	36	0.9
	3,965	100.0

DESIGN OF THE STUDY

The children of the tuberculous families under study were followed up for 5—24 years. The search for those who may have contracted tuberculosis was begun in 1969 and continued through 1970—1971 The total series of 4 025 cases was divided into the following groups according to the duration of follow-up

Follow up period	Year of birth	Number od cases
5—9 years	1960—1964	1 171
10—14 years	1955—1959	1 203
15—19 years	1950—1954	934
20—24 years	1945—1949	717
		4 025

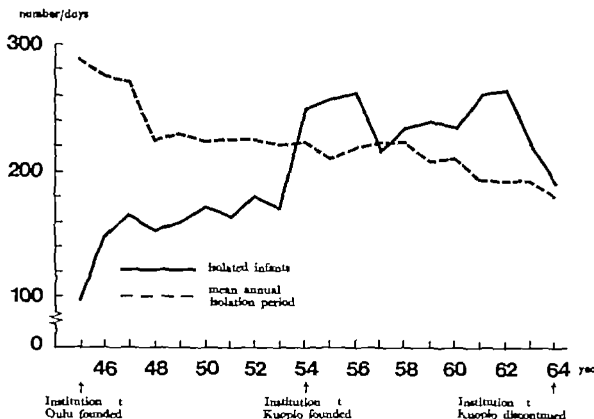
The search for the subjects who contracted tuberculosis was arranged in the following manner

1) Lists were compiled of the subjects treated in the institutions during 1945—1964 according to the tuberculosis districts to which they returned after isolation. These lists were then checked within each district if there were several offices in one district, each office went through the entire list for the district. Girls now of normal marriageable age were partly traced through their married names.
2) All the lists were checked against the central register of the National Board of Health, which has been kept since 1957
3) The official registers of causes of death compiled by the National Board of Health were controlled for the years 1945—1956 From 1957 the new above mentioned registration principle in Finland was introduced
4) The results of the follow up inquiries made by the institution at Tampere were controlled. The follow-up inquiries covered the children treated during 1945—1958
5) The results of the follow-up inquiries made by the institution at Oulu were similarly controlled These inquiries covered the children treated during 1945—1963
6) The surviving subjects who had contracted tuberculosis were invited to attend follow up examinations in the tuberculosis offices in different parts of Finland where the data on the subject and his family as well as earlier roentgenograms were available. Nearly all these examinations were carried out by the author and the clinical examination was supplemented by chest x rays and samples obtained for immunoglobulin and alpha 1-antitrypsin assays (71) The immunoglobulin values were compared with the normal values of each age group (52) Follow-up examinations were also performed on nine subjects who were preliminarily notified as being tuberculous, in the follow up inquiries made by the institutions but who had not been entered in the case records of the tuberculosis offices or other hospitals as having had tuberculosis. These nine were used as a control group for the immunoglobulin and alpha-1 antitrypsin assays.

PERIOD OF ISOLATION

The average period of isolation for the total series was 217 6 days. The periods of isolation per institution and year are shown in Table 12 and Figure 2. Only the subjects alive at discharge were included in the calculations of the period of isolation, i.e. the subjects who died from diseases other than tuberculosis, as well as those admitted for social reasons and those without BCG vaccination, are excluded from Table 12 and Figure 2 Since the introduction of BCG vaccination, the period of isolation has been about eight months, during the last few years of the study isolation period was clearly shorter in all the institutions.

Figure 2. The number of isolated infants per year and the mean annual isolation period during 1945—1964



BCG-VACCINATION

All the newborn isolated in nurseries were given routine BCG vaccination during the first few weeks the vaccine was administered and the reaction controlled according to the principles described by Ustved (103) If the newborn weighed less than 3 000 g on admission, vaccination was postponed untill the 3 000 g limit was reached A tuberculin test was made when vaccination was postponed, and the subject was vaccinated if his reaction was negative. The vaccine used was of the Swedish Gothenburg strain The vaccine was administered intracutaneously into the upper part of the left thigh

Seventeen infants of the total series were not vaccinated either because they had already been in contact with a tuberculous person, or because the parents claimed the newborn back so soon that there was no time for vaccination.

THE TUBERCULOUS MEMBER OF THE FAMILY

The tuberculous member of the family was in most cases the *mother* (59.2 per cent) Table 13 which shows the different family members as possible sources of infection, covers the total of 3 965 subjects treated according to the prophylactic principles. The estimates of the activity/inactivity of the disease are based on certificates issued by doctors of the tuberculosis districts and tuberculosis sanitariums.

There were 2,960 tuberculous mothers in the present series, and the mother was the only tuberculous member of the family in 2,346 cases. According to the information obtained from patient registers, case records and follow up cards 179 (6.0 per cent) of all the tuberculous mothers died of tuberculous immediately or soon after delivery

TRANSFER FROM THE INSTITUTION

After the specified period of isolation

TABLE 12.

THE AVERAGE ANNUAL ISOLATION PERIOD OF THE INFANTS TREATED IN INSTITUTIONS BETWEEN 1945 AND 1964.

	Tampere	Oul	Kuopio	Mean
1945	297.0	224.9		288.3
1946	247 4	329.2		274.9
1947	266.3	270.8		268.1
1948	209.7	238.9		222.5
1949	208.6	257.2		229.4
1950	220.2	223.2		221 7
1951	215.9	233.5		226.1
1952	208.8	240.0		223.5
1953	221 4	219.2		220.3
1954	200.1	230.2	239.5	222.7
1955	211.0	200.6	218.3	210.1
1956	211.6	219.7	225.5	218.9
1957	206.7	223.1	240.6	221 6
1958	210.8	213.7	252.3	223.4
19.9	207.8	190.1	232.3	207.5
1960	223.6	192.0	224.2	210.0
1961	193.0	176.7	225.0	193.0
1962	196.7	178.6	203.9	191 4
1963	184.3	198.9	193.7	192.6
1964	173.3	208.1	129.2	180.4
	215.7	217.6	222.0	217 6

the infant was either taken home or transferred to some other kind of care, depending on the statement of the physician of the tuberculosis district or tuberculosis sanitarium who reported the state of infectiousness of the home. The physician's instructions mentioned above were followed in most cases, but occasionally particularly if the father was the tuberculous family member the parents took their child home despite the risk of infection. Most of the infants discharged from the nurseries returned home, as can be seen from Table 14

TABLE 14

DOMICILE AFTER ISOLATION.

	No. of cases	
Home	3,131	79.0 %
Relatives	128	3._ %
Adoption	110	2.8 %
Foster home	122	3.1 %
Institution	303	7 6 %
Not known	3	0.1 %
Died while in the nursery	168	4.2 %
	3,965	100.0 %

TABLE 13.

THE TUBERCULOUS MEMBER O THE AMILY

	Activity of the disease	Number of cases		%
Mother	active	1 798	43.4	59.2
	inactiv	548	13.8	
Father	active	850	21.4	23.7
	inactive	93	2.3	
Both	active	161	4 1	15.5
	active in one, inactive in the other	313	7.9	
	inactive	140	3.5	
Other member activ or inactive		54	1 4	1 4
Not known		8	0.2	0.2
		3,963	100.0	100.0

SUBJECTS RETURNING TO TUBERCULOUS HOMES

Of the 3,965 subjects investigated, 279 were transferred from the nursery to a home where exposure to tuberculosis was certain according to the doctor of the tuberculosis district or sanitarium The other originally tuberculous homes were shown by bacteriological and/or radiological examinations to be non infectious at the discharge of the infant. The diagnosis of the family members of homes established as tuberculous was based on a bacteriological finding in 77 8 per cent of the cases and on a radiological finding only in 22.2 per cent of the cases.

The proportions of tuberculous members in such families are tabulated here

father	194	69.5 %
mother	76	27.2 %
other member	4	1 4 %
tw or more members	5	1.9 %
	279	100.0 %

The average period of isolation of those who returned to tuberculous homes was 254.3 days, compared to 217 6 days for the total series.

All the infants who returned to tuberculous homes were BCG-vaccinated but in *six cases* the current principles of BCG vaccination had not been followed (103) there was no tuberculin test before discharge in four cases, the tuberculin test before discharge was negative and no re-vaccination was performed in one case, and re-vaccination was performed a week before discharge in one case.

The reason for returning the infant to a tuberculous home could be ascertained in 2/3 of the cases from the case record data. These reasons are presented in Table 15 and they reflect to some extent the difficulties always encountered by medical staff working with tuberculous patients.

The number of infants returning to tuberculous homes has definitely decreased Of all those who returned to tuberculous homes, 168 (60 2 per cent) did so during 1945—1954 and 111 (39 8 per cent) during 1955—1964

NON BCG-VACCINATED

Among the children of tuberculous families isolated in institutions during 1945—1964 *17 newborn* did not have the

TABLE 15.

THE REASO FOR RETURNING THE IN ANT TO A TUBERCULOUS HO E.

	No. of cases
No foster home allable	50
Parents disobeyed instructions, taking their child home on their own responsibility	42
The tuberculous member of the family was given room of his own	21
The tuberculous member had applied for admission to a sanitarium, but had not been admitted before the infa t returned	6
The infant had healthy nurse at home	2
A seriously t berculous person was not admitted t sanitarium	8
Shortage of beds in institutions	3
The family had not eceived the financial aid due from the municipality	3
The tuberculous member of the family had been discharged infectious from sanitarium	3
The tuberculous member had refused sanitarium treatment	38
The t berculous member had been discharged from hospital as asocial	7
The t berculous member frequently isited home on holiday	2
The husband forced the mother to lea the sanitarium	1
The reasons were not pecified in the case record	93
	279

BCG vaccination and isolation. The omission of BCG vaccination was checked from birth reports, patient registers case records and follow up cards. All the newborn in this group were exposed to tuberculosis either after birth when the newborn was taken home through ignorance or for some other reason, or during the first few weeks of life when the parents took their infant home before it was BCG-vaccinated

STATISTICAL ANALYSIS

The morbidity and mortality risks of children born into tuberculous families were compared with the corresponding values for each age-group in the population at large by a test based on binomial distribution (9)

The groups within the series were compared using the χ^2 test.

The calculations were carried out on a Honeywell 1642 computer *

The results were analyzed at the Mathematics Department of the Technical Faculty University of Oulu

SUBJECTS RETURNING TO TUBERCULOUS HOMES

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The tuberculous member had refused sanitarium treatment	38
The tuberculous member had been discharged from hospital as asocial	7
The tuberculous member f equently visited home on holiday	2
The husband forced the mother leave the sanitarium	1
The reasons wer not specified in the case record	93
	279

TABLE 17

FREQUENCIES (%) OF BIRTH WEIGHTS IN THE DIFFERENT WEIGHT CATEGORIES ACCORDING TO THE ACTIVITY O THE MATERNAL TUBERCULOSIS AN THE PRESENCE TUBERCULOSIS IN SOME OTHER MEMBER O THE AMILY

	Mother active TB		Mother inactive TB		Other family member tuberculous, reference group	
	boys	girls	boys	girls	boys	girls
< 2,500	6.5	6.1	2.3	4.5	3.1	4.3
2,500—2,999	11.6	19.0	10.6	16.8	10.3	10.9
3,000—3,499	32.3	37.6	31.9	38.2	32.8	34.2
3,500—3,999	31 7	27.5	36.5	29.9	31 9	36.7
≥ 4 000	17.9	9.8	18.7	10.6	21 9	13.9
	100.0	100.0	100.0	100.0	100.0	100.0

TABLE 18.

MORTALITY FROM NON-TUBERCULOUS DISEASES DURING ISOLATION.

	Tampere	Oulu	Kuopio	Total	% of all those treated
1945	9	2		11	11 7
1946	4	3		7	4.8
1947	18	4		22	13.3
1948	4	5		9	5.9
1949	12	9		21	13.2
1950	6	9		15	8.7
1951	4	5		9	5.5
1952	9	13		22	12.2
1953	6	10		16	9 4
1954	4	2		6	2.4
1955	1	4		5	2.0
1956	2	1	1	4	1.5
1957	1	1		2	0.9
1958		2	1	3	1.3
1959		1		1	0.4
1960	3	3	1	7	3.0
1961				—	
1962		2	2	4	1.5
1963		1		1	0.5
1964	1	2		3	1 6
	84	79	5	168	4.2

Deaths in the institutions totalled 82 boys and 86 girls.
See Table 8.

Results

BIRTH WEIGHTS OF THE INFANTS BORN INTO TUBERCULOUS HOUSEHOLDS

There were 3 965 tuberculous families in the present series. Only the single births were included in the study of birth weights. Since there were 170 twins or triplets, the number of birth weights analysed was 3 795

The distribution of birth weights into the different weight categories was compared with that of a normal series of approx 12 000 single births collected in northern Finland in 1966 (86) The results are presented in Table 16

The proportion of premature infants was almost significantly higher among the children born into tuberculous families than in the reference series, and the birth weights of the infants born into tuberculous families were lower in general. When the two lowest and the two highest weight categories were combined the number of infants weighing less than 3 000 g was highly significantly greater in the group of tuberculous families than in the reference study and the number of infants weighing more than 3,500 g was highly significantly smaller

For a more detailed examination of the effect of maternal tuberculosis on the birth weight of the infant, the mothers were divided into the groups according to the activity of their tuberculosis, and the families in which the tuberculous member was other than the mother were used as a reference group. Again only single births were considered. The results for the different weight categories are presented in Table 17

Comparison of the results for the diffe

TABLE 16.

FREQUENCIES (%) OF BIRTH WEIGHTS IN THE DIFFERENT WEIGHT CATEGORIES COMPARED WITH ONE NORMAL FINNISH SERIES.

		Present series	Control series	Comparison
I	< 2,500	5.0	4.2	
II	2,500—2,999	13.4	11.0	
III	3 000—3 499	34.3	32.4	
IV	3,500—3,999	31 9	37.0	
V	≥ 4,000	15.4	15.4	
		100.0	100.0	

— almost significant
— significant
— highly significant

TABLE 19.

CAUSES OF THE DEATHS WHICH OCCURRED DURING THE ISOLATION.

	Total	%
Acute Gastroenteritis	61	36.3
Interstitial Plasma Cell Pneumonia	32	19.1
Other Respiratory Tract Infections	13	7.7
Septic Infections	11	6.5
Prematurity	16	9.5
Congenital Heart Disease	7	4.2
Jaundice	6	3.6
Asphyxia of the new-born	2	1.2
Cerebral Palsy	3	1.8
Acute Meningitis	1	0.6
Various Congenital Malformations	1	0.6
Whooping-cough	1	0.6
Cause of death not reported in the case record	14	8.3
	168	100.0

TABLE 20.

MORBIDITY AND MORTALITY FROM TUBERCULOSIS IN THE GROUPS INVESTIGATED.

	Number of cases	Late prognosis			
		Morbidity	%	Mortality	%
BCG-vaccinated	3,797	38	1.0	4	0.1
a) BCG-vaccinated, returned to non-tuberculous homes	3,518	16	0.5	2	0.06
b) BCG-vaccinated, returned tuberculous homes	279	22	7.9	2	0.7
Non-BCG-vaccinated	17	5	29.4	2	11.8

during isolation with general infant mortality.

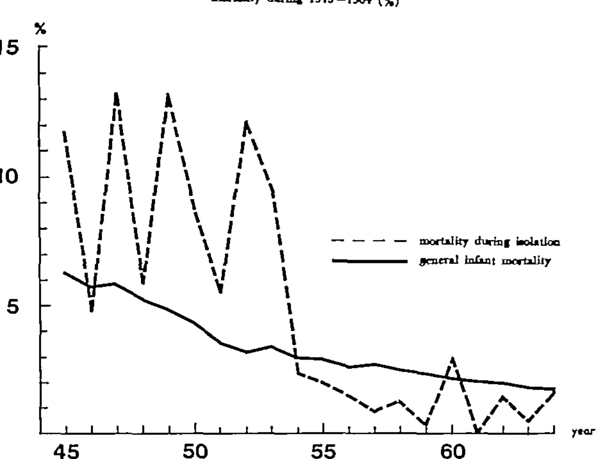
The causes of the deaths with occurred during isolation were obtained from the case records. As can be seen from Table 19 epidemic diarrhea and interstitial plasma cell pneumonia were the cause of death in 55 per cent of the cases.

MORBIDITY AND MORTALITY FROM TUBERCLOSIS

The follow up periods ranged from five to 24 years. The late prognosis for morbidity and mortality from tuberculosis in the cases followed up is given in Table 20.

In Figure 4 the BCG-vaccinated infants who acquired tuberculosis are classified according to the age at which the disease was contracted. the highest frequencies of infection occurred during the years immediately following isolation and at puberty. Most of those who contracted tuberculosis during the first years of life were infants returned to tuberculous homes.

There was no actual reference series in the present study. The results obtained



rent groups led to the following conclusions

— The number of premature infants in the maternal group with active tuberculosis was highly significantly greater than in the maternal group with inactive tuberculosis and significantly greater than among the non-tuberculous mothers. The mothers with inactive tuberculosis and the non tuberculous mothers displayed no statistically signigicant differences in the frequency of premature births.
— In the other birth weight categories the infants of mothers with active and inactive tuberculosis were not significantly different from each other
— The infants of mothers with active tuberculosis had highly significantly lower birth weights compared with the infants of healthy mothers, when the two lowest and two highest weight categories were combined.

The numbers of boys and girls born to the mothers with inactive tuberculosis and the healthy mothers were too small (10-20) to warrant comparisons between the sexes.

Mortality from non-tuberculous diseases during the stay in the institution

During the period of isolation in institutions, 168 infants died of diseases other than tuberculosis. Until 1953 mortality in the nurseries was noticeably high, but after that year it was lower than infant mortality in general. Mortality from non-tuberculous diseases during the period of isolation per year and institution is presented in Table 18 Figure 3 compares the non tuberculous mortality

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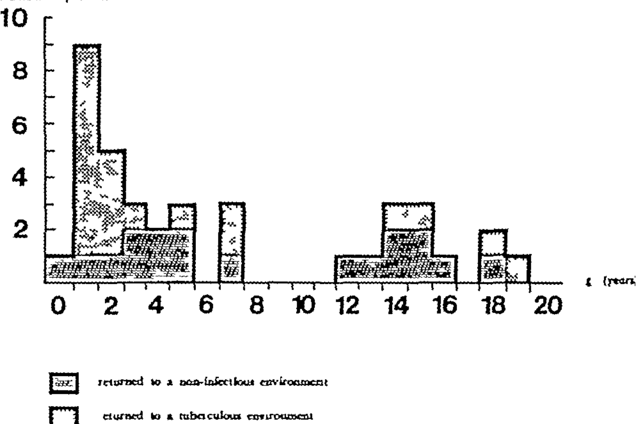
MORBIDITY AND MORTALITY FROM TUBERCLOSIS

The follow-up periods ranged from five to 24 years. The late prognosis for morbidity and mortality from tuberculosis in the cases followed up is given in Table 20

In Figure 4 the BCG-vaccinated infants who acquired tuberculosis are classified according to the age at which the disease was contracted the highest frequencies of infection occurred during the years immediately following isolation and at puberty Most of those who contracted tuberculosis during the first years of life were infants returned to tuberculous homes.

There was no actual reference series in the present study The results obtained

Figure 4 The ages at which the 38 BCG-vaccinated infants returned to infectious and non-infectious environment contracted tuberculosis



for the different groups were compared with the general tuberculous morbidity and mortality of the corresponding age group during the same period Comparison of the mortality figures is complicated by the fact that the general mortality from tuberculosis is expressed for groups comprising five age categories, and comparison of the morbidity figures suffers from the absence of statistics on tuberculosis in general for the period 1945—1951 The official tuberculosis register which has been kept since 1952 covers merely the new cases of respiratory tract tuberculosis, and only since 1966 has the occurrence of tuberculosis in other organs been officially recorded

The analysis of the late prognosis of children born into tuberculous families according to the present data and the above possibilities of comparison was as follows

1 The risk of mortality from tuberculosis among BCG-vaccinated infants born into tuberculous households during 1945-1964

	No. of infants	Died of tuberculosis	Ratio
BCG-vaccinated	3,797	4	1:950
General mortality from tuberculosis in the same age categories	1 825,708 *)	1 444	1 1260

*) Number of infants born during 1945–1964

Hypothesis Mortality from tuberculosis among children born into tuberculous families was the same as mortality from tuberculosis in the corresponding age categories of the population at large.

The hypothesis cannot be rejected at the risk level of 5 per cent, which means that birth into a tuberculous family did not increase the risk of mortality from tuberculosis.

2 The risk of morbidity from tuberculosis among children born into tuberculous households under the preventive principles generally employed in Finland during 1945—1964

	No. of infants	Contracted tuberculosis	Ratio
BCG-vaccinated infants returned to non-tuberculous environment	3,518	16	1:220
General morbidity from tuberculosis in the corresponding age categories	1,825,708	6,700	1:270

Hypothesis The risk of morbidity from tuberculosis among children isolated after birth, BCG-vaccinated and returned to non-tuberculous environment was the same as in the corresponding age categories of population at large.

The hypothesis cannot be rejected at the risk level of 5 per cent which means that the risk of morbidity from tuberculosis among the children born into tuberculous families was not greater than the risk in the corresponding age categories of the population at large, when the preventive principles outlined above were employed

3 The risk of morbidity from tuberculosis among BCG-vaccinated children born into tuberculous households regardless of the possible infectiousness of the domicile after the isolation period during 1945—1964

	No. of infants	Contracted tuberculosis	Ratio
BCG-vaccinated	3,797	38	1:100
General morbidity from tuberculosis in the corresponding age categories	1,825 708	6,700	1:270

Hypothesis Morbidity from tuberculosis among children born into tuberculous families was the same as in the corresponding age categories of the population at large.

The hypothesis is rejected at the risk level of 0.1 per cent (***) [illegible] means that children born into tub[illegible] families had a highly significant[illegible] risk of acquiring tuberculosis th[illegible] ren in the corresponding age categories [illegible] general

4 The effect of a tuberculous domicile on the risk of morbidity from tuberculosis among [illegible] vaccinated children born into tuberculous households during 1915—[illegible]

	No. of infants	Contracted tuberculosis	[illegible]
BCG-vaccinated children returned to non-tuberculous environment	3,518	16	1:[illegible]
BCG-vaccinated children returned to tuberculous environment	279	22	1:13

The χ^2 test showed that return to a tuberculous domicile increased the risk of morbidity from tuberculosis highly significantly (* * *)

5 *The effect of BCG vaccination on the risk of morbidity from tuberculosis among children born into tuberculous households during 1945—1964*

	No. of cases	Contracted tuberculosis	Ratio
BCG-vaccinated	3,797	38	1:100
Non-BCG-vaccinated	17	5	1:3

The χ^2 test showed that the protective effect of BCG vaccination against tuberculosis was highly significant (* *)

Isolation periods of the subjects who contracted tuberculosis

The average periods of isolation in the different groups were as follows

For all subjects who contracted tuberculosis	249 days
For subjects returned to tuberculous homes	261 days
For subjects returned t a non-tuberculous environment	233 days
For non-BCG-vaccinated subjects	62 days
For the total series	18 days

Socioeconomic background of the subjects who contracted tuberculosis

The socioeconomic background of the subjects who contracted tuberculosis was elucidated by interviews conducted by local public health nurses in the patients homes and by the author at the follow up examinations. The estimation of the economic status was based on the parents profession and their replies to the interviewers questions. The number of rooms and the number of people per room were taken as the criteria for the housing conditions. The socioeconomic background of BCG-vaccinated and non vaccinated groups was roughly as follows

	Economic status		Housing conditions	
	BCG+	BCG—	BCG+	BCG—
Good	2		4	
Satisfactory	21	1	15	1
Poor	11	2	15	2
Not known	4	2	4	2
	38	5	38	5

The six tuberculous subjects on whom there were no detailed data had all died of tuberculosis. The poor socioeconomic background was in most cases due to chronic tuberculosis some other disease or disability of the father Psychic stress occasioned by loss of the father of mother or problems experienced at puberty were reported in six subjects who contracted tuberculosis.

The state of infectiousness of the home before and at the onset of the disease

The state of infectiousness of the home in the cases of tuberculosis was ascertained by investigation of the card files and case records of the tuberculosis offices and by interviews conducted by local public health nurses in the patients homes and by the author at follow up examinations. The data obtained showed that nearly all of the subjects who contracted tuberculosis had had contact with open tuberculosis in their homes at some time between the end of isolation and the onset of their own disease. The state of infectiousness of the home before the onset of the subject s disease is shown below

INFECTIOUSNESS OF THE HOME	BCG+	BCG—
active tuberculosis	36	5
inactive tuberculosis	2	—
no tuberculosis	—	—
	38	5

The state of infectiousness of the home at the onset of the disease was slightly more favourable

INFECTIOUSNESS O THE HOME	BCG+	BCG—
active tuberculosis	25	5
inactive tuberculosis	11	—
no tuberculosis	2	—
	38	5

Concurrent disease at the onset of tuberculosis

Information on this point was obtained by interviews, from the tuberculosis offic es, and from the case records of tuber culosis sanitariums and other hospitals. Classical measles may have been the activating factor in two cases the other concurrent diseases are enumerated in Table 21

TABLE 21

CONCURRENT DISEASES AT THE ONSET O TUBERCULOSIS

	BCG+	BCG—
Respiratory tract infection	8	1
Measles	2	
Whooping-cough	2	
Diabetes	1	
Renal failure	1	
	14/38	1/5

The types of tuberculosis observed in the subjects

The form of tuberculosis most com monly encountered in the subjects was pulmonary tuberculosis. In four BCG-vaccinated cases with lethal tuberculosis the official cause of death was tuber culous meningitis. These deaths occurred in 1947 1949 and 1951 The other types of tuberculosis encountered are listed in Table 22.

TABLE 22.

THE TYPES O TUBERCULOSIS OBSERVED IN THE SUBJECTS

	BCG+	BCG—
Pulmonary tuberculosis	23	2
Tuberculosis of the tracheobronchial and mediastinal lymph nodes	9	1
Tuberculosis of the cervical lymph nodes	1	—
Tuberculosis of the bones and joints	1	—
Meningeal tuberculosis	4	1
Miliary tuberculosis	—	1
	38	5

) died of tuberculosis

The diagnosis of various forms of tuberculosis was more difficult at the beginning of the period under study, particularly in the 1940s, than later when patology and other similar methods were used to confirm the diagnosis. The diagnostic criteria for tuberculosis in all cases are presented in Table 23.

TABLE 23.

THE CRITERIA USED FOR DIAGNOSING TUBERCULOSIS

	BCG+	BCG−
Verification of bacteria	11/38	4/5
Radiological evidence	33/38	5/5
Tuberculin test (strongly positive or inversion)	21/38	5/5
Pathologico-anatomic evidence	5/38	2/5
Clinical symptoms	4/38	—
Treatment ex ivantibus	5/38	—

One non BCG-vaccinated infant who contracted tuberculosis at the early age of two months was examined for the possibility of congenital tuberculosis but no mesenteric calcified deposits were found at the follow-up examination. Reliable information obtained later from the maternity hospital proved that there had been contact between the infant and the mother immediately after birth.

Thirty-one (82 per cent) of the 38 BCG-vaccinated subjects who contracted tuberculosis were treated in tuberculosis sanitariums. The average duration of sanitarium treatment was 271 days.

Follow-up of tuberculous subjects

The follow-up examinations covered 28 of the 33 (five deaths excluded) BCG-vaccinated subjects who had contracted tuberculosis and three (two deaths excluded) of the non-vaccinated subjects. Clinical examination revealed nothing suggestive of tuberculosis. Radiological examination revealed hilar calcification in several cases, but no active tuberculosis. The immunoglobulin and alpha 1 antitrypsin values, given in appendix I and II were within the normal limits both in the study and control groups.

Discussion

GENERAL

When a newborn is infected with tuberculosis during delivery or when congenital tuberculosis is suspected, BCG-immunization is out of the question and chemotherapy remains the only possible method of treatment. A subject of great active interest is optimal prophylaxis of the other children born into the tuberculous family i.e., those who were not infected during delivery but who are exposed to a considerable risk of infection by a member of the family with active or chronic tuberculosis. The three possible methods are INH chemoprophylaxis, BCG-immunization and observation with regular tuberculin tests. No universal recommendation can be given, for there are several factors which affect the choice of the method, such as

— general incidence of tuberculosis in the country or the area in question,
— the activity of the mother's disease,
— the possible infectivity of the other members of the family
— the therapeutic regimen of the tuberculous family member (hospitalization /ambulatory on/off medication)
— the possibility of intrauterine infection or infection acquired in the lower birth canal during the course of delivery
— the socioeconomic status of the family (separate room nurse)
— the feasibility of BCG vaccination or INH prophylaxis in the family

The prophylactic measures taken to protect children born into tuberculous families against infection are often organized by the government, but, as can be seen from the factors affecting the choice of method the prophylactic regimen would often be better chosen *in casu*.

Mere *observation* with tuberculin tests is possible in countries where the *incidence of tuberculosis is low* A positive tuberculin test would then be a fairly reliable indication of infection, and tuberculin tests made at short intervals could be used to date the infection roughly However, frequent control visits might be inconvenient for some of the patients or parents, and inadequate control might lead to the development of primary tuberculosis into the postprimary phase.

B C G *vaccination* has so far proved to be the best method of protecting children of tuberculous families against infection and its efficacy has been demonstrated by several authors (61 89) The advantages of BCG vaccination include easy administration (one injection) satisfactory protection, and few complications. All the investigations of BCG vaccination of children of tuberculous families have shown it to have an undisputable protective effect. The degree of protection noted in the different studies varies considerably owing to the different strains of BCG vaccine used — their effects measured by tuberculin allergy may vary a great deal (15 45 117) — and the concentration and dosage of the vaccine. The method of administration has probably also affected the results.

One disadvantage of BCG vaccination is the separation of the infant from the mother for 6—8 weeks until the tuberculin test becomes positive. Attempts have been made to eliminate this disadvantage by developing an INH resistant strain of

BCG vaccine which would eliminate the need for isolation INH chemoprophylaxis would prevent infection and BCG vaccination would simultaneously bring about immunity (38) This method has not been successful at the international level, however for it has been difficult to develop such a strain of vaccine, as the International Union Against Tuberculosis; Committee On Prophylaxis stated in Moscow in 1971 (53)

One of the main disadvantages of BCG vaccination is the small value of the tuberculin test in the diagnosis of tuberculosis infection after BCG vaccination, particularly in regions where the incidence of tuberculosis is very low (6 93) Yet there are studies which show that the proper technique of performing the tuberculin test will partly solve this problem (3 65 92, 114)

Positive tuberculin tests due to other mycobacteria are already fairly common in e.g the United States (60) and the question has been discussed by Keay (59) and some other authors. Potentially pathogenic atypical strains have also been encountered in Finland (106) but they occur so infrequently (88, 106) that they can practically still be ignored

The actual complications of BCG vaccination, fatal generalized BCG infections, are exceedingly rare, and all the reports published have been on cases of immunological insufficiency (13 73 78) The immunological mechanism of such cases was last discussed by Sicevic (91) There are several reports of benign complications of BCG vaccination (e.g 113)

Chemotherapy has been established as the primary and basic method of treating tuberculosis in the last 20 years. Now that its effect in checking the destructive force of tuberculosis bacteria has been demonstrated in an ever increasing number of studies, a new promising concept for the control of tuberculosis has been created chemoprophylaxis. I have no control group which would have received chemoprophylaxis in the present study The immediate protective effect of chemoprophylaxis on newborn exposed to tuberculosis has been shown by Dormer et al. (28) The results obtained from mass examinations are not comparable with the findings of Dormer et al., but they do provide incontestable proof of the effect of chemoprophylaxis (35) When a child living in a tuberculous home which for some reason cannot be made non infectious is given INH prophylaxis against the continuous exposure to infection, the child develops no immunity The problem is what should be done after the home has become non infectious. Ferebee indicated that the protective effect of chemoprophylaxis continues after the therapy has been terminated (35) but even if it does, the more permanent protection of BCG vaccination deserves due attention. In Finland chemoprophylactic investigations have been carried out by Wasz Höckert and Salmi on newborn and infants (115) and Härö (48) and Tani (100) have discussed chemoprophylaxis in relation to the population at large.

Before chemoprophylaxis can be used as a routine therapeutic instrument, several problems remain to be solved

a) Motivation

Chemoprophylaxis is effective only when the drug is given regularly and in sufficiently large doses. If chemoprophylaxis is incomplete, the number of individuals discharging bacteria increases with the increasing risk of exposure Chemoprophylaxis is not successful in families with a gross social pathology (economic difficulties, no co-operation with public health officials, etc.) Co-operation with the lower social classes the disease of which tuberculosis is at the present, is often difficult and their problems of daily subsistence are frequently so acute and pressing that they have no time or energy to spare for the prophylactic treatment of a disease they may possibly get in the future. The observations of Sweet (99) on the success of chemoprophylaxis in the lower social classes are depressing He prescribed a chemoprophylactic program of one year s duration for 25 children of tuberculous families, and only two of them received the treatment for the whole year The most urgent pro-

blem in the development of chemoprophylaxis is therefore to find an effective and economic method of making chemoprophylaxis available to all those who really need it. This requires sociological research and financial support from the community

b) Degree of protection

The protection effect of chemoprophylaxis has been demonstrated (28 35) The degree of protection can probably be increased in two ways by increasing the dose or by prolonging the period of treatment. The dose of INH generally used has been 5 mg/kg body weight/day and the normal period of treatment 12 months. If the dose is increased there are more side-effects, and if the period of treatment is lengthened the number of subjects who take the drug regularly decreases. In two studies by Ferebee and Mount 64 per cent respectively 75 per cent of the subjects took their medication regularly for one year (36, 77) The degree of protection achieved in therapy of the newborn and infants depends on how well the parents understand the idea of prophylactic therapy and can be persuaded to give regular medication to a seemingly healthy infant. Resistance to INH has been considered another possible explanation for the failure of chemoprophylaxis.

Studies have been published on the occurrence of INH-resistant strains of bacteria following chemoprophylactic therapy (24) The bacteria acquired from the source may themselves already be INH resistant (10 94) It is therefore necessary to examine the antibiogram of the possible source of infection before introducing a chemoprophylactic regimen and to plan the treatment accordingly which is the general practice in pediatric hospitals in Finland. Simultaneous administration of another antituberculous drug would reduce the risk of resistance, but it would also add to the costs, make the medication more inconvenient, and increase the danger of toxicity Since children born into tuberculous families rarely discharge tuberculosis bacteria, the risk of developing INH resistance is very small, and there is thus no practical reason for combined chemoprophylaxis for children (42 118)

c) Newborn

Systematic studies of the immediate and long term effects of INH in protecting children born into tuberculous families against infection are actually very few (28, 110) Accurate dosage requires investigations of the serum INH content during the first few weeks of life, and the determination of acetylator phenotype would make even more individual dosage possible (72) The investigations done so far has revealed no side-effects (28, 110) INH is an antagonist of pyridoxine (80) and the neurological side-effects, in particular have been partly attributed to this fact. Pre-school and school-aged patients exposed to tuberculosis have displayed no side-effects during INH medication when given pyridoxine at the same time. INH chemoprophylaxis during the first month of life is not yet a routine measure, as has been pointed out by e.g Avery and Wolfsdorf (2) Cohen and Weber (18) and the Committee on Drugs, American Academy of Pediatrics (19) and BCG vaccination still appears to be safer The single injection compared with daily mediacation is a further point in favour of BCG vaccination.

DISCUSSION OF RESULTS

Birth weight of the infants born into tuberculous households

The present results show that more *premature* infants are born into tuberculous households than into other families, and that the *birth weights* of infants born into tuberculous households are lower than those recorded in the study from 1966 used as a reference series (86) It must be taken into account, however that the present series comes from a much earlier period than the reference series Comparable birth weight materials for 1945—1964 in Finland are not of technical reasons available. The frequency of premature births has declined during the last few decades, while he average birth weight of infants has increased so much that there are now no great differences between

the birth weights of infants born into tuberculous and other families. The frequency of premature births in the present series and the frequency of lower birth weights are both low compared with the findings of other studies. Monaco (76) and Rosenthal et al. (89) reported nearly the same results as the present ones.

The effect of maternal tuberculosis on the birth weight of the infants is clear, however, for the reference group used consisted of non-tuberculous mothers from the same period of time. The birth weights of the infants were highly significantly lower in the maternal group with *active* tuberculosis than in the maternal group with *inactive* tuberculosis and *non-tuberculous* mothers, and the frequency of premature births was highly significantly greater among the mothers with active tuberculosis. Other reports on the birth weight of infants born into tuberculous households have generally not distinguished between active and inactive maternal tuberculosis, which was the crucial factor in the present study. The effect of maternal tuberculosis on possible differences in birth weight between the sexes could not be clarified because the groups were too small for statistical analysis.

Mortality from diseases other than tuberculosis during isolation

Mortality from diseases other than tuberculosis during the period of isolation has been compared with general infant mortality (98) despite the fact that the mortality figures obtained account for only part of the infant mortality within the total series investigated. Figure 3 invites attention to the remarkably high mortality up to 1951, after which mortality during isolation has been lower than general infant mortality, as might be expected. There have been no great changes in the feeding of infants or the composition of the staff during the period of investigation, which means that the reasons for this great variation in mortality must be sought elsewhere. The following points may provide some explanation:

— The number of cases of influenza recorded in the official statistics is 4- to 8-fold in the years 1947, 1949, 1951 and 1953 compared with the intervening years. The frequencies of other respiratory tract infections and diarrhea differed only slightly in the years from 1947 to 1953 (96, 97).
— During the years 1952 and 1953 interstitial plasma cell pneumonia occurred in both of the nurseries then functioning; some of infants who died during the epidemics were autopsied.
— In 1953 major repairs were completed in the two institutions: automatic ventilation was installed, new methods of waste disposal and disinfection were established, the floors were re-surfaced and the woodwork painted.
— In 1954 a third institution for isolation of the newborn of tuberculous families was opened at Kuopio and the earlier shortage of space was thus eliminated.

The late prognosis of children born into tuberculous households in the light of the present results

Evaluation of the results for morbidity and mortality from tuberculosis is complicated by the numerous changes in the official tuberculosis statistics during the period under study. Comparison of the present results with the official statistics available provides the following *late prognosis for children born into tuberculous families*:

Mortality from tuberculosis: mortality from tuberculosis among children born into tuberculous families (4/3797) was not different from the corresponding mortality figures for the same age groups of the general population. The reference group consisted of BCG-vaccinated subjects born during 1945—1961.

The mortality figures obtained by other authors in similar studies, though with smaller series, are comparable with the present findings (61, 89, 110). None of the present subjects died from tuberculosis after 1951. The results obtained by

this method are clearly better than those obtained by isolation alone (11 61) The late prognosis of children born into tuberculous families and treated according to the prophylactic principles currently used in our country can be considered favourable as regards mortality from tuberculosis.

Morbidity from tuberculosis in the group treated according to the prophylactic principles employed in Finland morbidity from tuberculosis among those who returned to a non-tuberculous environment (16/3518) was not different from the corresponding morbidity figures of the same age-groups of the population at large The results obtained for this group represent the *actual late prognosis* of children born into tuberculous families who were isolated and simultaneously BCG-vaccinated. The present results show the late prognosis to be good. Rosenthal et al. carried out a nearly similar investigation, though the isolation period they used was clearly shorter, and reported the morbidity rate from tuberculosis to be 1.3 per cent, while the corresponding rate in the present study was 0.5 per cent (89) In the smaller groups studied by Wasz Höckert and Salmi and Kendig none contracted tuberculosis when the same method was used (61 110) The morbidity figures for the reference series during 1945—1951 had to be estimated. The estimate was based on the known morbidity figures of the different age groups from 1952 onwards. The infections in the reference group are cases of respiratory tract tuberculosis.

Morbidity from tuberculosis in the total series morbidity from tuberculosis in the total series (38/3797) was highly significantly greater than in the same age groups of the general population. The morbidity figures of the present study used in this comparison include the subjects who returned to tuberculous homes and subsequently developed tuberculosis. Thus, this figure for the total morbidity from tuberculosis in the present investigation does not provide a true picture of the late prognosis of children born into tuberculous households in Finland because the current prophylactic principles were not followed in all the cases.

Deviations from the prophylactic principles generally applied in Finland have led to poor results

— Morbidity from tuberculosis among those who *returned to tuberculous homes* (22/279) was highly significantly greater than among those who returned to a non tuberculous environment (16/3518) Six of the subjects who returned to a tuberculous environment had not been BCG-vaccinated according to the generally accepted principles, though they had received the BCG vaccine in some other manner but none of them contracted tuberculosis. In this group of families the tuberculous member of the family was strikingly often the father This seems to disprove the notion that the father is less dangerous as a source of infection. Morbidity from tuberculosis among those BCG-vaccinated subjects who returned to a tuberculous environment was clearly greater in the present study than in other similar studies (62, 68, 79) but it must be borne in mind that the number of subjects returning to a tuberculous environment may in reality have been slightly greater as has been pointed out by Kendig (61) It is therefore understandable that an infant must not be returned to a tuberculous home, and in cases where such a possibility threats the law on the protection of children in Finland allows the infant to be placed under guardianship even against the parents wishes (101)

— Morbidity from tuberculosis among the *non-BCG-vaccinated* subjects (5/17) was highly significantly greatter than in the BCG-vaccinated group (38/3797) Kendig reported a similar result 12 mothers were diagnosed as tuberculous only after delivery and the newborn were therefore in contact with their mothers without any protection one of them died of tuberculous meningitis and seven others con

tracted tuberculosis (61) This group of non BCG-vaccinated subjects, though it is small shows that it is advisable to continue BCG vaccination as a means of protecting children born into tuberculous families.

The purpose of the present study was to ascertain the effect of the prophylactic regimen generally employed in Finland on the late prognosis of children born into tuberculous families, and it can be seen that the late prognosis for tuberculosis is *favourable if the principles are followed* Several factors contribute to this favour able result

- Complete isolation from a tuber culous environment. The period of isolation has become shorter during the 20 years covered by the investi gation This is due to factors such as the new antituberculous drugs, which render the source of infection non infectious more quickly than before, and the general improve-ment in social and medical services. Rosenthal et al. showed that the isolation period can be shortened considerably (89)
- BCG vaccination was given to nearly every subject the reactions were controlled and re-vaccination was performed when necessary
- Tuberculosis offices and sanitariums were active in their attempts to render the tuberculous family mem bers non infectious.

To elucidate the reasons leading to the contraction of tuberculosis, *immunoglobu lins and alpha-l-antitrypsin were assayed in* cases of acquired tuberculous and nine control patients.

The increased risk of infection associat ed with agamma and hypogammaglobu linaemias is a known fact The immuno-logical pnenomena associated with tuber culosis are not yet fully known and the mechanisms can only be postulated (1) The sole purpose of the immunoglobulin assays in the present study was to detect the cases with manifest hypogamma globulinemia or agammaglobulinemia.

The immunoglobulin values obtained at the follow-up examinations naturally re-flect the immunological status of the sub ect only at the time of examination and thus, reveal relatively little of the situation at the onset of the disease, parti-cularly if the infection occurred during the first three years of life when the pro-duction of immunogobu ins may still have been rather inadequate (80) The results given in Appendix I show the real values obtained in mg/100 ml and these values are then compared with the normal values for the age group (52) No clear cases of immunological insufficiency were found though in one case of acquired tuberculosis IgG was 41 per cent of the normal for the age group

Alpha 1 antitrypsin is one of the three components of the alpha 1 fraction. Sev eral investigators have established a clear correlation between alpha 1 antitrypsin deficiency and chronic pulmonary disease (33 34) Eriksson noted alpha 1-anti trypsin deficiency in about 1 per cent of his subjects with chronic pulmonary disease (including asthma) (33) The mechanisms between alpha 1 antitrypsin deficiency and chronic pulmonary disease have so far been explained only theoretic ally

The average alpha 1 antitrypsin value was 220 6 mg/100 ml in the group of BCG-vaccinated subjects who contracted tuber culosis, 254 7 mg/100 ml in the non vaccinated group with acquired tuber-culosis, and 251 4 mg/100 ml in the control group These results show that the alpha 1 antitrypsin values of the subjects who contracted tuberculosis were normal

The prophylactic regimen employed in this study has certain *disadvantages* In 1971 the average cost of daily treatment was about $ 10 per isolated child The cost of chemoprophylaxis would be only a fraction of this. Another disadvantage is the average separation time of ?18 days from the mother The effect of this isolat ion on the mother-child relationship and the subsequent development of the child is outside the scope of the present investi gation, but this series would provide good opportunities for studying the long term effects of the interruption in the mother

child relationship the development of isolated infants could be investigated with special regard to growth (height and weight), school performance, frequency of psychiatric disorders and punishments given at school age and later

Prospects for the prophylaxis of children born into tuberculous households in Finland

This question is closely associated with the trends in the general incidence of tuberculosis, the alternative of terminating mass BCG vaccinations that has recently been considered in several countries, and the emphatic recommendations for the use of chemoprophylaxis (47) In countries where the incidence of tuberculosis is low mass vaccination is not necessary observation with regular tuberculin tests is enough and only certain risk groups are vaccinated. In Finland, where the incidence of tuberculosis continues to be high in comparison with the other Scandinavian countries, mass vaccination is still justifiable (48, 112)

Opinions concerning mass BCG vaccinations are similar in Sweden (23 32) and Denmark (70) It is advisable, however to re-appraise the situation at intervals of a few years, as Wasz Höckert and Härö have suggested (48, 112)

Chemoprophylaxis still involves several problems, and only when a sufficient number of controlled investigations have been published showing that chemoprophylaxis has favourable effects on the late prognosis and is not dangerous for the newborns will it be possible to consider the introduction of chemoprophylaxis as the sole method of protecting infants born into tuberculous households.

The number of children born into tuberculous households is clearly declining but one institution maintained by the Finnish Anti Tuberculous Association will probably continue to be necessary for approximately 10 years, after which the risk of morbidity from tuberculosis will be notably low according to Härö (49)

The objective must be to shorten the period of isolation in such a way that the interruption in the normal mother-child relationship is no longer than necessary for medical reasons. This is an objective that can be achieved by modern therapeutic methods.

Summary

The protection of children born into tuberculous households against infection is still an actual problem. The purpose of the present study was to elucidate the effect of the prophylactic regimen employed in Finland as shown by the late prognosis.

The study included 4 025 infants isolated in institutions during 1945—1964. The average period of isolation after birth was 218 days. BCG vaccination was performed during the first few weeks of life except in seventeen cases. The subjects were followed up for 5—24 years. The figures for morbidity and mortality from tuberculosis were compared with the official general morbidity and mortality statistics for the corresponding age groups of the population at large during the same period. *One per cent of the total series contracted tuberculosis and 0.1 per cent of them died of tuberculosis.* Of those who returned to a non tuberculous environment, 0.5 per cent contracted tuberculosis and 0.06 per cent died from it. Of those who returned to an infectious environment, 7.9 per cent contracted tuberculosis and 0.7 per cent of them died. In the non BCG-vaccinated group consisting of seventeen infats five acquired tuberculosis and two of them died.

Analysis of the results revealed following

- Birth into a tuberculous household did not increase the risk of mortality from tuberculosis, which concurs with the results of other studies in which infants born into tuberculous families have been isolated and BCG-vaccinated.
- Morbidity from tuberculosis among children born into tuberculous families was not different from the corresponding morbidity in the same age group of the population at large, provided the newborn are separated from the tuberculous source immediately after birth, BCG-vaccinated and returned to the home environment only when there is no more risk of infection.
- Birth into a tuberculous household increased the risk of morbidity from tuberculosis highly significantly according to the present findings, when the infants returned to tuberculous homes after isolation were included in the analysis.
- Morbidity from tuberculosis was highly significantly greater among non BCG-vaccinated subjects than among those who are BCG-vaccinated, but even the latter have relatively high morbidity figures in a tuberculous environment.
- Mothers with active tuberculosis gave birth to proportionate more premature infants and the birth weights of their infants were lower than those of mothers with inactive tuberculosis and healthy mothers.
- Mortality from diseases other than tuberculosis during the isolation period was much greater than general infant mortality up to 1954. The possible reasons are discussed.

The possible negative effect of isolation, maternal deprivation, was not studied.

The discussion concludes with a survey of the prospects of prophylaxis of children born into tuberculous families in Finland.

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APPENDIX I

IMMUNOGLOBULIN VALUES IN BCG-VACCINATED AND NON-VACCINATED PATIENTS AND IN BCG-VACCINATED CONTROLS, MG/100 ML AND PERCENTAGES OF NORMAL FOR CORRESPONDING AGES

BCG-vaccinated		IgG		IgA		IgM	
Case No.	Born	mg/100 ml	%	mg/100 ml	%	mg/100 ml	%
1	11 7.63	720	61	94	127	85	121
2	15. 2.62	[illegible]	97	74	100	78	110
3	12.12.61	860	79	440	595	86	121
4	6. 3.61	580	53	120	162	49	69
5	[illegible]0.12.60	980	85	115	137	86	113
6	11 5.59	1050	92	190	226	92	121
7	25.10.57	680	54	170	168	82	94
8	11 3.56	640	51	68	67	130	149
9	4.11.54	800	66	170	163	190	164
10	10. [illegible].54	760	63	150	144	210	181
11	16. 6.53	1050	87	115	111	170	147
12	18. 7.52	840	70	400	385	120	103
13	30. 5.52	1050	87	40	231	260	224
14	27 3.52	1500	124	240	231	420	362
15	30. 1.52	1000	83	400	384	140	121
16	3.10.51	840	70	110	106	92	80
17	26. 8.51	500	41	105	100	62	53
18	24 5.51	1200	99	100	96	96	82
19	21 11.50	980	81	110	106	145	125
20	16.11.50	1600	133	190	183	150	130
21	5. 8.49	700	58	160	154	92	80
22	5. 7 49	1000	83	240	231	92	79
23	17 2.49	720	60	110	106	230	198
24	9 9.48	1050	87	140	135	230	198
25	27 5.47	860	71	140	132	200	172
26	4. 2.47	760	61	140	132	150	130
27	2. 2.47	760	61	400	384	43	37
28	19 12.46	860	71	110	106	130	112

Non-BCG-vaccinated							
Case No.	Born						
1	20. 7.60	1000	87	74	68	110	145
2	30. 5.59	740	62	100	108	115	152
3	29. 5.56	960	77	100	99	140	161

BCG-vaccinated controls							
Case No.	Born						
1	18. 7 62	700	64	68	92	76	107
2	6. 5.61	1500	131	170	202	120	158
3	8. 2.59	860	75	64	76	76	100
4	11 10.57	1050	85	48	47	92	105
5	21 11.56	540	43	86	85	56	64
6	31 3.54	720	60	78	75	76	66
7	18. 1 49	680	56	110	105	130	112
8	9 9.48	760	61	115	111	140	121
9	13. 7 46	1250	104	400	384	130	112

APPENDIX II

ALPHA-1 ANTITRYPSIN VALUES [IN] BCG-VACCINATED AND NON-VACCINATED [P]ATIENTS AND IN BCG-VACCINATED CONTROLS, MG/100 M[L]

BCG-vaccinated

Case No.	Born	mg/100 ml
1	11 7.63	196
2	15. 2.62	224
3	12.12.61	189
4	6. 3.61	217
5	20.12.60	252
6	11 5.59	224
7	25.10.57	164
8	11 3.56	210
9	4 11.54	224
10	10. 2.54	217
11	16. 6.53	168
12	18. 7.52	196
13	30. 5.52	224
14	27 3.52	265
15	30. 1.52	232
16	3.10.51	217
17	26. 8.51	301
18	24. 5.51	175
19	21.11.50	259
20	16.11.[illegible]0	217
21	5. 9.49	301
22	5. 7 49	189
23	17 2.49	168
24	9. 9.48	169
25	27 5.47	245
26	4. 2.47	245
27	2. 2.47	210
28	19.12.46	280

Non-BCG-vaccinated

Case No.	Born	
1	20. 7.60	238
2	30. 5.59	294
3	29 3.[illegible]6	232

BCG-vaccinated controls

Case No.	Born	
1	18. 7.62	168
2	6. 5.61	434
3	8. 2.59	329
4	11 10.57	265
5	21 11.56	224
6	31. 3.54	232
7	18. 1 49	203
8	9. 9 48	203
9	13. 7 46	232

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*From the Institute of Pediatrics, School of Medicine, and the Institute of Probability
School of Statistics, University of Rome, Rome, Italy*

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INTRODUCTION

There is general agreement that in symptom free low-weight newborns the systemic systolic blood pressure (SBP) is lower the lower the weight, and increases after birth (9 26 27 32, 34 36, 38, 42, 47 68) A correlation *with the gestational age (GA) has* been *found* by some investigators (26, 27 36), not by others (32, 38) In general, it can be stated that the quantitative relationships of SBP with body weight, GA, and post-natal age have not been satisfactorily evaluated, preventing not only a better understanding of physiological mechanisms regulating the SBP in the newborn, but also a proper evaluation of SBP changes in abnormal conditions.

In the present study the relationships of SBP with body weight, GA, post natal age, and arterial Hematocrit (Ht) were calculated by means of multiple regression analysis in symptom-free low-weight newborns during the first four days of birth. Using these standards, the SBP changes in low weight newborns with the respiratory distress syndrome (RDS) were evaluated. Finally a longitudinal study was performed on the SBP changes in the first three weeks of life.

METHODS

Measurements

The SBP was measured indirectly by a xylol-pulse indicator instrument (1) modified by us (9) (Fig. 1) The plastic cuffs (46) were 2.5 cm wide All determinations were performed on the unrestrained arm, usually in the semi flexed position, with the baby lying supine inside the incubator and were repeated several times until minimal variations around a steady baseline were observed. Measurements were made at some distance from meals, and with the baby quiet or asleep

In order to measure the aortic blood pressure, a No 5 open-ended catheter (Argyle*) was inserted for 6–8 cm into an umbilical artery and connected, through a 3-way stopkock, to a pressure transducer (Sanborn, 267 series) with the zero level at the mid-axillary line. Pressure was recorded on a direct writing Sanborn electronic oscillograph. Calibration was performed by the mercury manometer included in the xylol instrument The catheter was frequently flushed with saline and the pulse pressure was closely watched, since the constance of pulse pressure after flushing was considered as the best indication that no obstruction of the catheter had previously occurred.

The GA was calculated from the first day of the last menstrual period, and rounded to the nearest week. Birthweight percentiles for GA were calculated according to the single birth, sex specific intrauterine weight chart of Lubchenco et al. (39). The Ht was measured on the arterial or on arterialized capillary

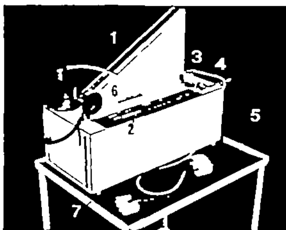


Fig 1 The instrument. 1) Oblique mercury manometer 2) the glass pulse-indicator showing a xilol droplet in the capillary 3) two ways stopcorck; 4) obstructing cuff 5) pulse sensing cuff; 6) bubble level, 7) levelling screws. (For correct readings, the platform must be kept horizontally and the level of mercury in the reservoir must be kept constant).

* Supplied by Thackray Ltd., London, England.

Table 1 *Difference (Δ) of SBP between right and left arm (indirect method), and between indirect (arm) and direct (aortic) SBP in simultaneous measurements*

Comparison	No. of cases	Body weight (kg, range)	Post-natal (age, range)	Total no. of comparisons	Indirect SBP (mmHg, range)	Δ SBP (mmHg, $m \pm$S.D.)
Right-left arm SBP (indirect)	10	0.94–1.90	1–19 days	100	41–87	-0.01 ± 2.8
Indirect-aortic SBP	5	1 16–2.72	14–30 hours	50	43–66	-0.5 ± 1.4

blood after centrifugation of capillary tubes at 4 000 r p.m. for 5 min. (Studies from this laboratory showed that, in 28 simultaneous determinations performed in the first four days of life the Ht of "arterialized" capillary blood was 3.2 ± 2.4% higher than in arterial blood.) Acid-base and oxygen determinations were performed on arterial or "arterialized" capillary blood by means of a micro-Astrup apparatus and a Clark type micro electrode. Carbon dioxyde tension (P_{CO_2}), oxygen tension (P_{O_2}) and pH were corrected for the temperature of the baby *Right to-left shunt* was calculated from arterial P_{O_2} when breathing oxygen at a concentration higher than 80% Additional details on methods of sampling, measurement and calculation have been given elsewhere (10, 48)

Statistics

In order to analyze the quantitative relationships between SBP body weight, GA, post natal age and Ht, we used basically a multiple regression equation where SBP was the dependent variable Since in our case it was not possible to choose *a priori* the functional form of the equation we adopted a polinomial model, and a main part of the problem was the determination of the degree and only subordinately the numerical evaluation of the parameters. Several tests were performed for evaluating the behaviour of the adopted model (see Statistical Appendix, section 1)

The evaluation of results in particular groups of individuals was based on the analysis of the residuals (r), i.e on the comparison of the values

rSBP = observed − predicted SBP (mmHg)

for each individual (see Statistical Appendix, section 2.1)

Other standard statistical tests (χ^2 test, Student's t-test, analysis of variance for randomized blocks, Scheffe's multiple comparison test) were used either in exploring the validity of the model, or in examining some special problems (see Statistical Appendix).

SUBJECTS AND RESULTS

The babies were admitted to the Premature Unit within 48 hours of birth (91% within 24 hours), and placed in closed incubators at ambient temperature of 31–34 C, according to clinical conditions and to rectal temperature. The standard clinical examination included recording of the respiratory rate, Silverman's score, and skin colour every 3 hours for at least 2 days, and less frequently thereafter

Comparison of SBP measurements, right vs. left arm (indirect), and indirect vs. aortic

In each one of 10 subjects, 10 simultaneous measurements of indirect SBP were performed in the right and left arm by independent observers. In 5 other babies with severe RDS, 10 simultaneous measurements of indirect and intrarterial (aortic) SBP were also obtained. Results have been shown in Table 1

In both comparisons, the mean of algebraic (i.e. sign considered) differences in simultaneous measurements was very small and of course statistically not significant, showing no systematic difference between indirect SBP in right and left arm, or between indirect and

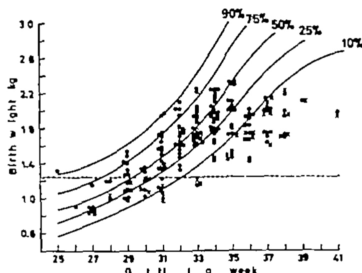


Fig. 2. Birthweight and gestational age of symptomfree infants, plotted against the intrauterine weight chart (single birth, sex non specific) of Lubchenco et al. (39). Explanation of symbols: open and black circles = infants considered in the regression analysis with body weight, gestational age, and postnatal age; black circles = infants considered in the regression analysis with hematocrit as additional predictor variable; crosses = additional infants with birthweight < 1 250 g and/or < the 10th percentile for gestational age, considered in the analysis of *r*SBP reported in Table 3.

aortic SBP. The standard deviation of differences was also small, indicating a reasonably good agreement between simultaneous measurements. Results were similar in subjects with above or below median SBP levels, weight, or post natal age.

Symptomfree subjects

Characteristics of subjects. Considered as symptomfree were all babies with a respiratory rate below 60–65 in the first two days of life and below 55–60 thereafter, a Silverman's score always below 3, and no cyanosis, marked jaundice, or other abnormalities in the period of the study. Chest films, taken in 78% of them, showed at most a mild decrease in over-all transparency of lung fields and/or very mild patches of atelectasy. They received standard incubator care, were starved in the first day of life, and were given by oro-gastric tube 25-50-75 ml/kg of pooled human milk in the second, third, and fourth day respectively. They all survived the newborn period.

The multiple regression analysis of SBP according to body weight, GA, and post-natal age (3–96 hours). 189 subjects were considered; their birthweight ranged from 0.86 to 2.30 kg, and their GA from 25 to 41 weeks (Fig. 2). On them, 651 SBP determinations were performed between 3 and 96 hours of birth.

The quantitative relationships between SBP on the one hand, and body weight, GA, and post-natal age on the other, were studied by a multiple regression analysis. The best regression equation from point of view of fit and simplicity was:

$$\text{SBP, mmHg} = 23.20 + 8.13x_W + 0.503x_{GA} + 0.226x_{PA} - 0.00160x_{PA}^2 \quad (1)$$

(where x_W = body weight, kg; x_{GA} = GA, weeks; x_{PA} = postnatal age, hours)

Predicted values of SBP for different values of x_W, x_{GA}, and x_{PA} have been calculated from equation (1) and have been reported on Table 2. The partition of the SBP predicted in an hypothetical baby into the various components (from 3 to 96 hours of age) has been graphically illustrated in Fig. 3.

The inclusion in equation (1) of higher degree terms (i.e. the quadratic terms x_W^2, x_{GA}^2, or the cubic terms x_W^3, x_{GA}^3, x_{PA}^3), and of interaction terms (i.e. the terms $x_W \cdot x_{GA}$, $x_W \cdot x_{PA}$, $x_{GA} \cdot x_{PA}$) did not improve significantly the fit. On the other hand, the elimination from equation (1) of a term whatsoever reduced significantly the fit.

The estimated standard deviation of single measurements was 6.8 mmHg. (This is a measure of the natural variability of the phenomenon, and includes the effect of all ran-

Table 2. *Predicted SBP (mmHg) in symptomfree low-weight newborns from 3 to 96 hours of age calculated after equation (1)*

The thick contour includes values pertaining to the area of body weight/gestational age characteristics of the population in the study

Body weight, kg	Gestational age, weeks 27	28	29	30	31	32	33	34	35	36	37	38	39	40
0.80	43	44	44	45	45	46	46	47	47	48	48	49	49	50
0.90	44	45	45	46	46	47	47	48	48	49	49	50	50	51
1.00	45	45	46	46	47	47	48	48	49	49	50	50	51	51
1.10	46	46	47	47	48	48	49	49	50	50	51	51	52	52
1.20	46	47	47	48	48	49	49	50	51	51	52	52	53	53
1.30	47	48	48	49	49	50	50	51	51	52	52	53	53	54
1.40	48	49	49	50	50	51	51	52	52	53	53	54	54	55
1.50	49	49	50	50	51	51	52	52	53	53	54	54	55	55
1.60	50	50	51	51	52	52	53	53	54	54	55	55	56	56
1.70	51	51	52	52	53	53	54	54	55	55	56	56	57	57
1.80	51	52	52	53	53	54	54	55	55	56	56	57	57	58
1.90	52	53	53	54	54	55	55	56	56	57	57	58	58	59
2.00	53	53	54	54	55	56	56	57	57	58	58	59	59	60
2.10	54	54	55	55	56	56	57	57	58	58	59	59	60	60
2.20	55	55	56	56	57	57	58	58	59	59	60	60	61	61
2.30	55	56	56	57	57	58	58	59	59	60	60	61	61	62
2.40	56	57	57	58	58	59	59	60	60	61	61	62	62	63

Add for a post-natal age of

Hours	3–7	8–12	13–18	19–24	25–32	33–40	41–54	55–89	90–96
mmHg	1	2	3	4	5	6	7	8	7

dom disturbances which in any case prevent the actual results to fit exactly the theoretical model.) The estimated standard error of the predicted value was approximately of 0.9 mmHg. (Actually this value is a function of the given levels of weight GA, and post-natal age, with calculable coefficients, and therefore it is not constant. However in the present analysis, the numerical values for the practical ranges of the independent variables did not differ appreciably from the value given above.) More precise details have been given in the Statistical Appendix, section 1

SBP and arterial Ht The possible relationship of SBP with Ht was also investigated by *multiple regression analysis, which included* simultaneously body weight, GA, post natal age, and Ht as predictor variables. Determinations were performed on part of the babies considered in the previous paragraph, and were included only when the time lapse between blood sampling and SBP measurement had been not longer than 2 hours for babies in the first day of life, and not longer than 8 hours for older subjects. 251 sets of values (blood Ht mean 59.1±6.7% range 40–79%) from 93 subjects (whose birthweight and G.A. has been shown on Fig. 2) were considered. The inclusion of terms with Ht (i.e. x_{Ht}, $x_{Ht} \cdot x_W$, $x_{Ht} \cdot x_{GA}$, $x_{Ht} \cdot x_{PA}$, $x_{Ht} \cdot x_W \cdot x_{GA}$, $x_{Ht} \cdot x_W \cdot x_{PA}$, $x_{Ht} \cdot x_{GA} \cdot x_{PA}$, $x_{Ht} \cdot x_W \cdot x_{GA} \cdot x_{PA}$, x_{Ht}^2) into a linear model and into a quadratic model was proven statistically not significant in order to predict SBP values (see also Statistical Appendix, section 1.2).

SBP and sex[1] Out of the 651 determinations used for the calculation of equation (1), 282 had been performed in 86 males, and 369 in 103 females. The means and standard deviations of *r*SBP from males and females were

[1] In this and in most of the following analysis the SBP values have been expressed as residuals (*r*SBP), i.e. the difference, in mmHg, between the observed value and the value predicted according to equation (1) (see also Statistical Appendix, Section 2.1).

calculated separately and, as shown on Table 3 were found to be practically identical, indicating that the model was equally valid in males and in females.

SBP in classes according to weight percentile for GA In order to check whether the predictor variables with x_W and x_{GA} were valid throughout the whole range of observed weight/GA relationships, the *r*SBP from symptomfree babies were grouped into 6 classes according to birthweight percentile for GA, and the mean and s.d. were calculated (Table 3). Since the number of observations in babies with a birthweight < the 10th percentile for GA, used in the calculation of equation (1), was relatively small (122 determinations in 38 subjects), 85 additional determinations in 31 symptomfree babies (age 3–96 hours) who had been studied subsequently were included Their birthweight and GA has been shown in Fig 2.

As reported on Table 3 with the exception of results in the group above the 90th percentile, in the remaining groups the mean *r*SBP was very close to 0 and the differences between the groups were small and statistically not significant. In the group with birthweight < the 10th percentile the mean *r*SBP was also calculated at various post natal age intervals, and no significant differences from predicted values were found.

SBP in newborns with very low weight The validity of equation (1) in babies with a birthweight < 1 250 g was checked by considering separately 97 determinations from 25 such subjects, used in the calculation of the equation, to which 41 determinations from 13 symptomfree individuals, who had been studied subsequently were added. Their birthweight and GA has been illustrated in Fig. 2. The mean and S D of *r*SBP has been reported on Table 3 showing no appreciable difference from predicted values. Also in this group the mean *r*SBP was calculated at various post natal age intervals, and no significant differences from predicted values were found.

The SBP changes after birth. As shown in Fig. 3 it was calculated by multiple regression

Table 3 *Mean ± S.D of rSBP (i.e. SBP residuals: actual-predicted SBP) in groups of symptomfree low-weight newborns (age 3–96 hours)*

Group	No. of cases	No. of observations	*r*SBP mmHg (mean ± S.D)
By sex			
Males	86	412	−0.2 ± 6.6
Females	103	369	0.0 ± 7 1
By post-natal age, h			
3–12		107	−0.4 ± 7.9
13–24		114	−1 1 ± 6.6
25–48		198	+0.9 ± 6.9
49–72		143	+1 1 ± 5.6
73–96		89	−1.9 ± 6.5
By weight percentile			
> 90	7	19	+3.6 ± 5.3
76–90	15	38	−0.5 ± 5.3
51 75	41	120	−1.5 ± 6.6
26–50	56	230	0.0 ± 6.9
11 25	32	120	+0.2 ± 6.3
< 10[a]	69	208	+0.1 ± 6.5
Birthweight			
< 1.25 kg[b]	38	138	−0.5 ± 6.6

[a] Including 85 observations from 31 "new" babies.
[b] Including 41 observations from 13 "new" babies.

analysis that the SBP increased more rapidly in the early hours of the period of observation, and then progressively more slowly- a peak was reached by the end of the third day followed by a slight decrease in the fourth day of life. Predicted changes were of +4 mmHg from 3 to 24 hours of life +2.5 mmHg in the second day +1.2 mmHg in the third day and −1.2 mmHg in the fourth day The validity of predictor variables with x_{PA} in equation (1) was checked by calculating the mean and s.d. of *r*SBP at 3–12 hours, 13–24 hours, 2, 3 and 4 days of age (Table 3) a satisfactory fit was found in the first three days of life whereas in the 4th day the mean of *r*SBP was slightly but significantly ($p < 0.05$) lower than expected, suggesting that at the latter age the average SBP actually decreased more than predicted from equation (1)

It was attempted to check the validity of the equation in the first two hours of life but unfortunately too few SBP determinations were available at such age in symptomfree subjects. With respect to SBP changes after the

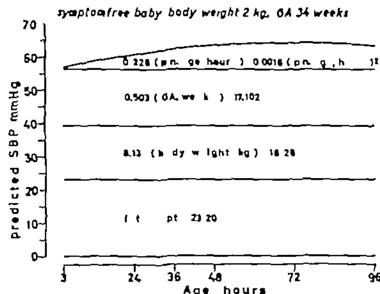


Fig 3 Graphical representation of the predicted SBP (and of predicted SBP component) in an hypothetical symptomfree baby (body weight: 2 kg; gestational age: 34 weeks) from 3 to 96 hours of age.

4th day of life, equation (1) described a progressively greater decrease of SBP and, obviously could not be extrapolated to such ages. In addition, body weight was not a suitable predictor variable to study SBP changes over a long period of time, since the error due to post natal weight variations was introduced. Therefore in order to evaluate the average SBP variations during the early weeks of life, the SBP was measured in 36 symptomfree babies (birthweight, mean 1.67 range 1.0–2.2 kg GA, mean 33.3 range 27–41 weeks) at 1 3–4 10 and 20 days of age. Throughout this period, the SBP increased on the average by about 15 mmHg, at a faster rate in the first 10 days of life, and more slowly thereafter (Fig. 4 A) The over-all increase, and the increase from 3–4 to 10 days of age were found significant ($p < 0.001$) by appropriate statistical tests (see Statistical Appendix, section 2.2). The SBP increment at 10 and 20 days of age was not significantly different in subjects with above or below median birthweight, and in infants with a birthweight above or below the 10th percentile for GA (Fig 4 B and C)

Patients with RDS

Characteristics of subjects. All babies with a Silverman's score always higher than 2 in the first 2 days of life were considered as affected by RDS. 106 subjects with known GA, with

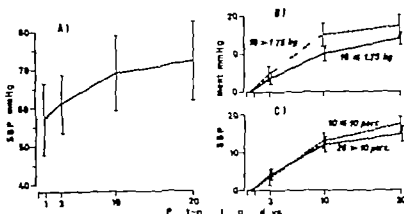


Fig 4 Longitudinal study on SBP in 36 symptomfree low-birth weight babies from 1 to 20 days of age. (A) Mean ±S.D. of SBP in the whole group. (B) and (C) Mean ±S.E. of the SBP increment with respect to the first day value in. (B) 18 subjects with birthweight > or < the median value of 1 75 kg, and (C) 10 subjects with birthweight < the 10th percentile for gestational age, and in 26 subjects with higher percentile.

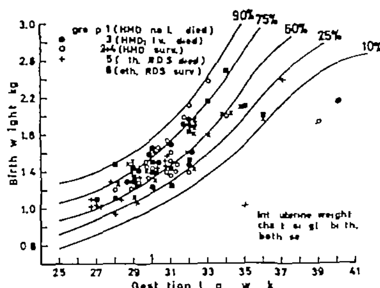


Fig. 5. Birthweight and gestational age of infants with RDS, plotted against the intrauterine weight chart (single birth, sex non-specific) of Lubchenco et al. (39).

birthweight between 1.0 and 2.5 kg, and who had been studied for the first time at 3–12 hours of age, were selected for the study. The birthweight and GA of the patients, classified as explained below, has been shown in Fig. 5. Chest films were always taken on admission, and were classified retrospectively as follows: 1) severe abnormality = diffuse fine granularity and/or marked and diffuse decrease in transparency of lung fields, 2) absent or mild abnormality = absence of findings listed under 1). (Patients with other severe abnormalities, such as diffuse coarse nodularity, pneumothorax etc., were not included in this series.)

All babies received supplemental oxygen (from 40 to 100% concentration) for at least 2 days, and usually longer. In part of the cases only oral feeding was given by oro-gastric tube, starting in the second day of life. The remaining subjects received intravenously 70 ml/kg/day of 10% glucose solution, and sodium bicarbonate as required to correct for the Base Deficit. In subjects with severe X ray abnormality treatment was given according to three different programs: 1) in the first part of the investigation, only oral feeding was given, 2) in the second part, patients were randomly treated by oral feeding or by intravenous infusion (55); 3) in the last part, babies were always given intravenous infusion therapy. As to babies without severe X ray abnormality intravenous therapy was administered to 33% of cases, and usually to patients more severely affected from clinical or laboratory point of view. Respirator treatment was never administered.

Out of the 63 newborns with severe X-ray abnormality 37 died. Post mortem examination was performed in 33 patients. Intracranial hemorrhage was found in 48% and pulmonary hyaline membranes in 79% of the patients. 17 out of 43 subjects without severe X-ray abnormality died, and post mortem studies were available in 16. The incidence of intracranial hemorrhage was 69% and of pulmonary hyaline membranes 12%.

SBP changes according to X-ray findings treatment and outcome. It was assumed that a comparison between babies who did or did not receive intravenous therapy was warranted only for the patients with severe X ray abnormality since they had been assigned to either therapy without consideration of the severity of the disease. On the contrary this requirement was not met in patients without severe X-ray abnormality who were therefore not separated according to treatment.

In view of this consideration, 6 groups were

Table 4 *Characterization of groups of babies with RDS*

No of group	Chest film finding	I.v therapy	Outcome	No. of cases
1	Marked abnormality	No	Death	18
2	Marked abnormality	No	Survival	10
3	Marked abnormality	Yes	Death	20
4	Marked abnormality	Yes	Survival	16
5	Abs. or mild abnormality	Yes & no	Death	17
6	Abs. or mild abnormality	Yes & no	Survival	26

separated (Table 4), and the mean and S.D of *r*SBP was calculated in each group at various post natal age intervals. Values in group 2 and 4 were very similar and were therefore pooled. The results have been reported in Table 5 and illustrated on Fig. 6

In the groups of babies with RDS and severe X ray abnormality (i.e. the patients with Hyaline Membrane Disease, groups 1 to 4) the mean of *r*SBP was always significantly lower than expected during the first 3 days of life The lowest average values were observed in the babies who died (groups 1 and 3) After the age of 12 hours, on the average there was no change in the group with intravenous infusion (group 3) as compared to a slight—but not significant—decrease in untreated babies (group 1) This suggested, although did not prove conclusively that the infusion was able to prevent to some extent the deterioration of SBP levels. Mean values in survivors (groups 2+4) were only mildly decreased, and returned to normal by the fourth day of life.

When considering babies without severe X ray abnormality early values were markedly and significantly lower than normal only in the group of patients who died (group 5), not in survivors (group 6) In the former group, very low mean values were found during the whole period of observation. In the latter group, the mean level was significantly lower than expected only at 13–24 hours of age.

SBP changes according to arterial pH P_{CO_2} and Hematocrit and to right-to-left shunt In part of the patients with RDS, SBP measurements were performed simultaneously" (i.e. with a time lapse of less than 2 hours) with determinations of arterial pH P_{CO_2}, and Hematocrit, and with estimation of the right-to-left shunt. However when significant amounts of alkali were given between the SBP and the acid-base determinations, values were not considered. From 3 to 48 hours of age, 167 SBP measurements simultaneous with pH (pH 7.29±0.09 range 7 02–7.51), 164 with P_{CO_2} (P_{CO_2}, mmHg: 47 6±14.9 range 21–145), 156 with Hematocrit (Ht% 54 7±9.5 range 30–80), and 93 with right-to-left shunt (r-l shunt % 37.5±14 1 range 12–72) were available. As a first step, pH, P_{CO_2}, Ht, and right to-left shunt values were plotted against *r*SBP in

Table 5 *Mean ±S.D (and no of observations) of rSBP in various groups of subjects with RDS*

	Postnatal age				
Groups	3–12 hrs	13–24 hrs	25–48 hrs	49–72 hrs	73–96 hrs
1	−8.3±7.3 (*18*)	−11.1±4 6 (*7*)			
3	−6.9±6.8 (*19*)	−7.3±8.7 (*12*)	−7.6±7.2 (*10*)		
2+4	−4 4±5.2 (*26*)	−4.8±5.4 (*22*)	−4 7±4.8 (*25*)	−3.5±4.9* (*23*)	−1.1±5.2 (*22*)
1+2+3+4[a]	−5.9±7 1 (*63*)				
5	−5.7±7.0 (*17*)	−10.8±5.7 (*14*)	−10.3±8.0 (*14*)	−10.4±4 1 (*5*)	
6	−1.0±9.5 (*26*)	−3.5±7.3 (*20*)	−2.7±6.4 (*23*)	−2.7±7.1 (*24*)	−1.9±4 6 (*18*)
5+6[a]	−2.9±8.8 (*43*)				

Always before intravenous infusion.
Significance of difference of means from expected values (by Student's *t*-test): $p<0.05$ $p<0.01$
Significance of difference of means between groups 5 and 6 (age 13–24 hours and 25–48 hours): $p<0.01$

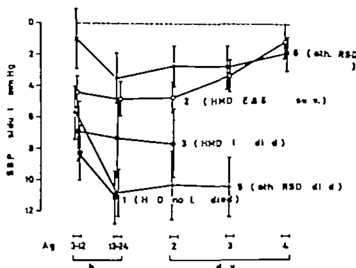


Fig 6 Mean ±S.E. of *r*SBP (i.e. predicted – actual SBP mmHg) in groups of infants with RDS at various postnatal age intervals.

three different age groups (3–12, 13–24 and 25–48 hours), and considering separately babies with or without severe X ray abnormality who did or did not receive intravenous infusion prior to measurement, and who died or survived: inspection of the plots did not suggest any likely correlation. In addition, the incidence of marked hypotension (i.e. *r*SBP < −10mmHg) was calculated in patients with higher or lower arterial pH, P_{CO_2}, and right-to-left shunt: as shown in Table 6, no relevant differences were observed. In view of these findings, no further statistical evaluation was pursued

The prognostic significance of SBP changes. In consideration of the average *r*SBP differences between babies who died or who survived, an attempt was performed to assess the prognostic significance of *r*SBP values in the first day of life. Inspection of the results at various intervals of *r*SBP showed that the mortality rate was remarkably higher among subjects with *r*SBP below −10 mmHg than in those with higher values, whereas no consistent changes in mortality rate were apparent when considering various classes of *r*SBP above −10 mmHg. Therefore only two classes of *r*SBP were considered for comparison (Table 7)

Residuals below −10 mmHg were obtained in 25% of patients at 3–12 hours, and in 36% of cases at 13–24 hours of age When considering the total population of patients with severe X ray abnormality (groups 1 to 4), the mortality rate was approximately doubled in the class with lower *r*SBP and the differences were statistically significant by χ^2 test. Similar results were observed also in subjects without severe X-ray abnormality (groups 5+6), but the difference was statistically significant only at 13–24 hours of age. In patients with severe X-ray abnormality the mortality rate was higher than in subjects without severe X ray changes and with comparable post natal age and *r*SBP levels, but the differences were never

Table 6. *Incidence of severe hypotension (i.e. rSBP < −10 mmHg) in patients with RDS (age 3–48 hours) according to arterial pH arterial* P_{CO_2}, *and right-to-left shunt*

	No. of cases	% rSBP < −10 mmHg
pH		
>7.20	143	30.1
<7.20	24	33.3
P_{CO_2}, mmHg		
>60	29	31.0
<60	135	29.6
Right-to-left shunt		
>50%	17	35.3
<50%	76	27.6

Table 7 *Mortality rate in various groups of babies with RDS and with or without severe hypotension at 3–12 and 13–24 hours of age*

	RDS groups							
	1+2		3+4		1+2+3+4		5+6	
*r*SBP	No. of cases	% died	No. of cases	% died	No. of cases	% died	No. of cases	% died
Age								
3–12 hours								
< −10 mmHg	7	100	9	67	16	81	10	60
> −10 mmHg	20	50	27	52	47	51	33	33
13–24 hours								
< −10 mmHg	5	80	9	67	14	71	13	69
> −10 mmHg	11	27	15	40	26	35	21	24

Significance (by χ^2 test) of differences between subjects with *r*SBP < −10 mmHg or > −10 mmHg: $p<0.05$ $p<0.01$

significant. When considering subjects with severe X ray abnormality there were no significant differences in mortality rate between groups with comparable *r*SBP levels and who did or did not receive intravenous infusion therapy but the number of observations was too limited to allow definite conclusions.

DISCUSSION

Methodology

Our modifications to the instrument originally deviced by Ashworth et al. (1) were found convenient in order to make measurements easier and more accurate. The accuracy (reproducibility) of SBP measurements was not checked by repeated measurements on the same arm (this would not have been correct, in view of the spontaneous SBP variations with time (28)), but rather by simultaneous measurements in the two arms. Since no systematic difference was shown between right and left arm, the difference between simultaneous measurements could be considered as an estimate of errors in the technique By this approach, a reasonably accuracy was observed.

The comparison between indirect and intrarterial SBP can be considered as an estimate of the precision of the indirect method. In keeping with previous work with the same technique (18, 45) or with electronic oscillometry (47), an excellent agreement was found.

In symptomfree subjects analysis of *r*SBP by subgroups (Table 3) (and additional calculation reported in the Statistical Appendix, section 1) never showed relevant discrepancies from predicted values in various sections of the population considered. Furthermore, in the same subjects the statistical analysis (Statistical Appendix, section 1 6) did not demonstrate individual trends to higher or lower than expected SBP levels. We may therefore conclude that the statistical model was adequate. Nevertheless, a relatively large variability was found. SBP changes, either spontaneous or associated with changes in activity (28), may account at least in part for this variability

Weight gestational age and SBP

The multiple regression analysis showed that in symptomfree low weight newborns the SBP could be predicted more accurately when considering simultaneously weight and GA than when considering either of these factors alone, and that the SBP increased linearly with both such variables. This relationship was also valid in babies with very low weight, and in subjects with severe intrauterine growth retardation as well as in infants with birthweight up to the

90th percentile for GA. Some difference from predicted values was found only in babies with birthweight above the 90th percentile for GA, but this finding cannot invalidate our results, since in this group the number of observations was small, and presumably the GA had been often grossly underestimated.

In view of these results, it was felt warranted to calculate isopleths for SBP (i.e. lines connecting points with the same SBP at various weight/GA cohordinates) These have been shown in Fig. 7 and clearly illustrate predicted SBP changes with weight and GA. Isopleths drawn as interrupted lines were calculated for a population not included in the present study and obviously need to be checked experimentally However it is interesting to remark that the predicted SBP extrapolated at normal term (i.e. at GA of 40 weeks, weight of 3.2 kg, and post-natal age of 12 hours) was 71.8 mmHg, a figure which is well in keeping with the mean values of 67–73 mmHg found by most previous Authors by indirect (27 32, 34 38) or by direct (42, 62, 69) methods in healthy full-term babies in the first day of birth.

The increase of SBP with GA (and hence with maturation) is not surprising, and will be discussed in greater detail in the following paragraph. On the other hand, the significance of the SBP increase with weight is open to question. In first place, it cannot be excluded that SBP truly depends only on GA, and that the relationship with weight, found by regression analysis, was due to the fact that, to some extent, the weight can be a better index of the true GA than the calculated GA. This because the first day of the last menstrual period can be reported erroneously or because conception can occur at various distance from this date. Unfortunately there is no way to test this hypothesis. A second possibility would be that the lower pressure in subjects with low weight for GA was due to the inclusion in the symptomfree population of subjects with severe malnutrition, which is known to give hypotention in the young rat (23). However this

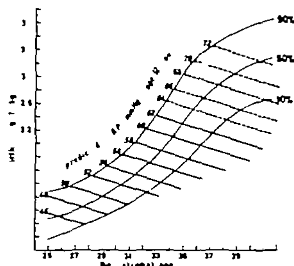


Fig 7 Isopleths of predicted SBP according to weight/gestational age cohordinates in symptomfree newborns with a postnatal age of 12 hours. Isopleths at birthweight above the 90th percentile for gestational age have been omitted. Interrupted lines indicate isopleths extrapolated to populations not included in the present study

seems unlikely because statistical analysis showed that at any given GA the SBP increased linearly with weight up to the 90th percentile for GA. It seems therefore likely that in low weight newborns the SBP truly depends on weight as well as on GA, and this is supported by the observation, reported by Dawes (22), that in full-term lambs with accurately timed length of gestation the blood pressure was higher the higher the weight. (He did not find this correlation in pre-term lambs, but the range of weight was so narrow that no conclusion could really be drawn) As a final hypothesis, also the correlation of SBP with weight could be interpreted in terms of maturation. In fact, it has been assumed that maturation is a function not only of time but also of the rate of growth, the smaller individuals being in general less mature than larger subjects with the same GA (40).

Developmental changes of SBP

The present findings can give us a more complete understanding of SBP changes occurring

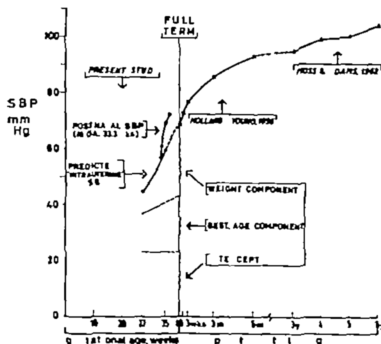


Fig 8 Average course of "intrauterine and postnatal SBP according to the present and to other studies. Other explanations in the text.

during development. A tentative representation of the mean course of SBP in the early period of life has been illustrated in Fig. 8. On this diagram the mean intrauterine" SBP was calculated as the sum of the intercept of the GA component and of the weight component according to equation (1), whereas the post-natal age component was not included. (It is fully recognized that such intrauterine" blood pressure inferred from post-natal observations, can hardly be identical to actual levels occurring prenatally but it is reasonable to assume that the rate of increase would be similar) The median weight according to the intrauterine growth chart of Lubchenco et al. (39) was used in order to calculate the weight component from 27 to 40 weeks of GA. The interrupted SBP lines indicate extrapolated values, since no term babies with appropriate weight were included in this study As to the mean post-natal SBP the two largest studies available in the first six years of extrauterine life were reported in Fig. 8 these were the data by Holland & Young (32) in the first 6 months of life and those by Moss & Adams (41) from 3 to 6 years (the latter were the median values between those reported in males and females) It appears from Fig. 8 that the SBP increases rapidly in the first year of conception and much more slowly thereafter and that most of the fast rise occurs within full term of gestation. In the latter respect the human species seems to differ from all other mammalian species so far studied, including the rhesus monkey where the first rise occurs prevalently after birth (22)

No satisfactory explanation can be given for the slow increase of SBP throughout late childhood and adolescence (41), but it is generally admitted that the fast rise in the early period of conception is basically due to maturation of the autonomic nervous control (22, 41) The subject has been recently reviewed by Dawes (22), who concluded that the evidence for this process was satisfactory in the lamb but still scanty in the human species. In any case it has been shown that in healthy pre-term newborns the peripheral vascular resistance is lower than in full-term subjects (13 35 52) This allows peripheral blood flow to be maintained in spite of the relatively low blood pressure, and may contribute in turn to keep the blood pressure levels low Therefore the low blood pressure of pre-term fetuses appears

perfectly adequate to steady intrauterine conditions. On the other hand, in view of the role played by the autonomic function in the maintenance of homeostasis in independent life and in abnormal conditions (12), it seems likely that in the very premature fetus and newborn the capability for circulatory homeostasis is remarkably limited.

SBP changes in the early post-natal period

The SBP changes in the early minutes of birth were not investigated in the present work, but previous studies in healthy full-term newborns have shown relatively higher values in the first minutes of life, which decreased until the age of 2–4 hours, and which have been attributed to the mild asphyxia of normal birth (3 18, 45 62) However this fall was not found in healthy premature newborns (45) The subsequent increase has been repeatedly reported (9 18 38, 42) and has been quantitated in the present study

Inspection of Fig. 8 suggests that in the early days of birth a transient acceleration of the SBP increment occurs both in full-term (32) and in low-birthweight (present study) symptomfree babies. Perinatal hemodynamic changes, such as the interruption of placental circulation and the closure of the Ductus Arteriosus (2, 22), increasing oxygen consumption (30, 56), and enhanced sympathetic activity (15) may all play a role in this phenomenon.

The lack of correlation between SBP and arterial Ht in newborns with low weight

There are two reasons why one would expect a positive correlation between SBP and Ht in the newborn. In the first place, a striking increase of blood viscosity occurs with Ht higher than 50–60% (4 50); therefore, unless compensatory mechanisms should simultaneously come into action, under such circumstances a rise of blood pressure should occur in order to keep constant the peripheral blood flow Secondly in low-weight newborns the venous Ht was directly related to blood volume (61) and in experiments of short duration in full-term newborns the blood pressure increased with hypervolemia and decreased with hypovolemia (63–65 69) therefore, Ht and blood pressure should also be related. In fact Buckels & Usher (11) reported that, in full-term newborns, late clamping of the umbilical cord—a procedure presumably increasing the blood volume (44)—was followed by higher Ht and higher pressure than when the cord was clamped immediately after birth (but these Authors determined the flush —not the systolic—blood pressure, and the capillary—not the arterial—Ht)

On the other hand, it has been pointed out in a recent review (51) that with moderate variation of blood volume the changes in blood pressure are slight because of concomitant adjustments of peripheral vascular resistance and that marked hypotension occurs only in the terminal stages of hemorrhagic shock. This might explain why in our symptomfree babies, in whom presumably very marked blood volume changes did not occur in the neonatal period, no correlation was found between SBP and Ht levels. However such correlation was lacking also in our series of babies with RDS. It has been suggested that in newborns with RDS and/or the post asphyxial state hypotension is due to hypovolemia (29 49) which results from fluid transudation out of the vascular space, and is therefore associated with increasing Ht levels (49) A fluid shift from the vascular compartment in the early hours of birth has been reported by other investigators also in full term and premature babies without RDS (17 24) In view of these possibilities, no definite meaning can be given to Ht levels as an index of blood volume in distressed newborns and therefore no conclusion can be drawn on the lack of correlation between Ht and SBP values, observed in the present study

The SBP in low-weight newborns with RDS

It has been generally admitted that in newborns with RDS the blood pressure is often

abnormally low (and more markedly in patients with fatal disease) (5 9 16 29 43, 45 49 53 57 58) but the lack of appropriate reference standards has so far prevented a quantitative evaluation of changes with respect to healthy controls. This was accomplished in the present study by comparing values in sick babies to those predicted by multiple regression analysis in symptomfree subjects. In this investigation, hypotension was found on the average throughout the acute phase of the disease it disappeared in survivors by the fourth day of life· in agreement with a previous report (45) showing a rapid SBP drop in the early minutes of birth, it was already present at the age of 3–6 hours, it was more marked in babies who died and, at variance with a previous study (58) it was so already in the early hours of birth. When patients who died or survived were considered separately no marked differences were observed between subjects with or without Hyaline Membrane Disease.

In order to interpret these findings, circulatory changes occurring in acute asphyxia and hypoxia should first be considered. In arterial hypoxia two main patterns are usually identified (37), an high output pattern, characterized by peripheral vasodilatation, tachycardia, increased systemic flow and slight hypotension, and a low output one, with increased peripheral vascular resistance, bradycardia, decreased cardiac output, and hypertension. The latter presumably results from more severe and/or sustained oxygen deficit, and allows a preferential redistribution of blood flow to vital organs. Studies in the newborn, both animal and human, have been recently reviewed (8, 22, 37) Contrasting findings have been reported but, as a rule in the newborn acute asphyxia has been rapidly followed by bradycardia and hypotension (6, 20 21 33). Peripheral vascular resistance was found to increase (13). Cardiac output was not systematically altered in some studies (19 54 60), but was reportedly decreased in lambs with hypoxia associated to non respiratory acidosis (37) In human newborns with severe RDS similar changes have been observed, with markedly increased peripheral vascular resistance (66) and decreased cardiac output (16, 66). The observation that the difference between arterial and capillary pH and P_{CO_2} was greater in distressed than in healthy newborn babies (25) also suggests poor peripheral perfusion in the former group.

The similarities of circulatory changes in acute asphyxia and in severe RDS do not necessarily mean that changes in RDS are due to hypoxemia and acidemia in the course of the disease Stahlman et al. (58) reported that in RDS blood pressure increased after alkali administration and with high oxygen as compared to low oxygen breathing. In the present investigation (as well as in a controlled trial from this Center on a group of patients partly included in the present series (55)) a limited beneficial effect of alkali administration was possibly observed, but hypotension was by no means corrected. In addition, the incidence of marked hypotension was similar in patients with or without severe acidemia, hypercarbia, and right-to-left shunt. Similar findings have been reported by others (29). In consideration of the complex interactions of respiratory and non-respiratory acidosis and of hypoxemia on the circulation (37) it is fully recognized that more studies are needed in order to define the possible relationship of such changes to hypotension in RDS. However the present evidence suggests that in most circumstances arterial acid-base and oxygen changes in the course of RDS have a limited effect on blood pressure and that hypotension, although possibly initiated by perinatal asphyxia, is subsequently maintained by other mechanisms.

In view of the considerations given above, it seems likely that in RDS severe hypotension is associated with increased peripheral vascular resistance and decreased cardiac output This assumption should be substantiated by further investigation but, if this were the case the possible role of hypovolemia (29 49), decreased return of venous blood to the heart (16) or im-

paired myocardial function (37) should be considered. The nature of the increase in peripheral vascular resistance needs also to be elucidated. The hypothesis of an altered peripheral arteriolar response to cathecolamines (14) deserves consideration, since a similar event has been postulated in endotoxin shock, a condition in which many circulatory and metabolic abnormalities similar to those encountered in RDS occur (31). In any case it must be emphasized that the circulatory changes discussed above presumably occur only in part of the babies with RDS, since in the present series hypotension was by no means constant, and since marked abnormalities of peripheral vascular resistance and of cardiac output were not found in patients with mild disease (66). In the present investigation hypotension, although related to outcome, was not related to other unfavourable prognostic factors such as acidemia, hypercarbia and right-to-left shunt (7, 59). This suggests that, in part of the newborns with RDS, circulatory abnormalities relatively independent of pulmonary insufficiency play a critical role in death or survival. In view of the present results and speculation, more studies on cardiac function and peripheral circulation in RDS seem justified.

SUMMARY

The systemic systolic blood pressure (SBP) was studied by an indirect method (using a xylol-pulse indicator instrument) in low-birth-weight babies. Simultaneous measurements of indirect SBP in the right and left arm, and of indirect and aortic SBP documented a satisfactory reproducibility and precision of the indirect method.

In 186 symptomfree subjects, a multiple regression analysis on 651 SBP determinations from 3 to 96 hours of age showed that SBP was independently related to body weight, gestational age (GA) and post-natal age. A multiple regression equation was therefore calculated, showing that SBP increased linearly with weight and GA, and non-linearly with post-natal age and enabling to quantitate expected SBP values in symptomfree low-weight babies from 3 to 96 hours of age. The prediction was equally valid in males and females, in various weight percentile classes up to the 90th percentile for GA (including 69 subjects with marked intrauterine growth retardation), and in 38 subjects with birthweight of 0.86–1.25 kg. No correlation with arterial Hematocrit was evidenced by multiple regression analysis on 251 SBP determinations from 91 symptomfree subjects, including this parameter as an additional predictor variable. A tentative representation of developmental SBP changes from fetal life to childhood was presented by combining present results, extrapolated to pre-natal conditions, with other studies in the literature. This suggested that, at variance with other mammalian species, in the human the fast developmental rise of SBP occurs mostly before birth and, in addition, that in the early postnatal period a transient acceleration of the SBP increment occurs. In the interpretation of these findings, the possible role of maturation of the autonomic nervous control has been emphasized.

In comparison with expected values, results in 107 low-weight newborns with RDS (including 64 patients with X ray diagnosis of Hyaline Membrane Disease), showed on the average hypotension in the early hours of birth, which persisted or even increased throughout the acute phase of the disease, and disappeared by the fourth day of life in survivors. Hypotension was associated with poor outcome, but not with severe acidemia, hypercarbia, right-to-left shunt, or changes in arterial Hematocrit. The infusion therapy with glucose and $NaHCO_3$ possibly prevented a further SBP drop after the early hours of birth. Although the interpretation of these findings appeared difficult, it was suggested that in RDS hypotension was not primarily due to concomitant acidemia and hypoxemia, and that the elucidation of mechanisms leading to hypotension may contribute to identify lethal

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STATISTICAL APPENDIX

L. Piccinato

In the following pages will be described. (1) the method by which a regression function of the SBP over other controlled variables has been determined (sec. 1), (2) the statistical procedures employed in order to analyse some particular aspects of the problem (sec. 2).

1 *Determination of the regression equation*

1.1 (*Methodology*) A regression approach, after some preliminary analyses by means of standard ANOVA *techniques*, has been performed. For sake of simplicity we shall use the following notations:

x_1 = postnatal age, (*hours*)
x_2 = body weight, (kg)
x_3 = gestational age, (weeks)
x_4 = hematocrit.

The x_4 variable is available only for a group of items, which we shall call "A" group in opposition to "B" group, without a measure of hematocrit (Ht).

At first, a second order model has been determined containing 15 parameters. Since we had the Ht among the predictor variables, only 251 measures were available. Symbolically we assumed.

$$E(y)=\beta_0+\beta_1 x_1+\beta_2 x_2+\beta_3 x_3+\beta_4 x_4 \qquad (A\,1)$$
$$+\beta_{11}x_1^2+\beta_{22}x_2^2+\beta_{33}x_3^2+\beta_{44}x_4^2$$
$$+\beta_{12}x_2 x_1+\beta_{13}x_1 x_3+\beta_{14} x_1 x_4$$
$$+\beta_{23}x_2 x_3+\beta_{24}x_2 x_4+\beta_{34}x_3 x_4$$

After getting the estimates of the parameters (by least squares method) we tried to simplify the equations by considering two possibilities: (I) to eliminate Ht as a predictor variable (II) to eliminate the interaction effects (β_{12}, etc.)

1.2 (*Reduction of the model*) The aforesaid possibilities are equivalent to the following statistical hypothesis:

$$\beta_4=\beta_{44}=\beta_{12}=\beta_{13}=\beta_{14}=\beta_{23}=\beta_{24}=\beta_{34}=0 \qquad (A\,2)$$

The procedure for the control is given by the well known partial *F*-test,* and is based on the normality and common variance assumptions for the data, around the "true values" provided theoretically by (A 1). The analysis is given in Table A 1

Since $F=1.65$ (with 8 and 236 degrees of freedom) is not statistically significant at 10% level, the hypothesis (A 2) is not contradicted by the data, so that the model can be correspondently restricted. The fitted reduced model is

$$y=-136.82+0.212x_1-0.0013x_1^2-25.84x_2$$
$$+10.06x_2^2+11.66x_3-0.1654x_3^2. \qquad (A\,3)$$

It will be called, in the following, "quadratic additive model"

1.3 (*Further analysis on the quadratic additive model for the A group*). Some aspects of the quadratic additive model have been furtherly investigated in order to evaluate (I) the opportunity of including cubic terms (without interactions) (II) the possibility of reducing the model to a linear one (with respect to the independent variables) which would be more useful *from a practical standpoint*.

The first problem involves the choice between the equation (A 3) and an equation based on a model such as:

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* For reference see e.g. N. R. Draper, H. Smith: *Applied regression analysis*. John Wiley, New York, 1967

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BY KARIN STENSLAND JUNKER

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From the Departments of Pediatrics and Audiology of Karolinska Institutet at Karolinska Sjukhuset Stockholm, S eden

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by

KARIN STENSLAND JUNKER

ALMQVIST & WIKSELL
Stockholm

To BENGT JUNKER

CONTENTS

NOTICE

The double pagination aims at making the orientation easier to the reader. Every chapter has an initial letter used for the interior indication of pages, tables and figures, so that the reader know to what chapter a referral belongs. The ordinary pagination is not usually referred to only when there is no interior pagination.

For want of settled norms regarding spelling, syllabication, abbreviations, punctuation, and denominations, etc., the author has tried to follow Webster's Seventh New Collegiate Dictionary 1969 as far as possible.

The current name of the child health centers in U.S.A. has been applied. Well-baby clinics, abbreviated WBC.

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PREFACE

A request made in 1965 by Bengt Barr M.D associate professor and head of the Department of Audiology at Karolinska sjukhuset, initiated this investigation. We knew from the very start that this would be a long-term project, since the problem was connected with the growth and educational development of very small children.

Methods of screening communicative disorders as early as possible in infancy had been required for a long time The experience of the child audiology clinic showed the difficulties connected with achieving a diagnosis regarding indifference to acoustic stimulance when organic hearing, from the physiological viewpoint, is intact.

We felt that prospective programs even for infants with other disorders than organic hearing defects had to be the next step in the plans to furnish non-communicative children with a functioning means of communication. Thus, our inspiring cooperative efforts which had started already early in the fifties were renewed, for which I am deeply grateful.

I wish to extend my deep thanks to the chief of the Ear Nose-and-Throat clinic at Karolinska sjukhuset, professor Carl-Axel Hamberger M.D., head of the Department of Otolaryngology for his interest and valuable support. Professor Claes-Christian Elert, Ph. D., Umeå University gave me helpful suggestions regarding the first part of the investigation which was presented to the Institute of Linguistics, Department of Phonetics, Stockholm University in 1968

However the investigation would never have been carried through without the personal encouragement and indispensable support given to me by professor John Lind, M.D., head of the Department of Pediatrics, Karolinska sjukhuset. The unusual generosity with w has shunned no efforts in helping and advising me has made it me to fulfill the investigation.

As a result of our cooperation, I feel that a closer link between the audiological, pediatric, psychological educational, social, and linguistic approach to communicative disorders in children has been made possible which is highly promising for the future within this inter disciplinary field.

Long ago when my late husband's interest for the handicapped, and especially the communicatively disturbed children was awakened, he felt it self-evident to get in touch with professor Lennart Holmgren, M.D at that time head of the Department of Audiology Karolinska sjukhuset, and Erik Wedenberg, M.D., professor of audiology Karolinska institutet. Many of their fruitful thoughts about abberating communication in children have been gratefully utilized during the course of my work.

Without the broadminded help and patience of my close friend and colleague as one of the leaders of Lekoteket på Blockhusudden* Evy Blid it would have been impossible to accomplish the study She has not only given me ingenious impulses, but also taken over the responsibility for the management of our advisory bureau for training through play activity when I was tied up with the final trials and editorial work.

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doctors, nurses and their assistants, as well as the staff of the nursery homes at Klingsta, Danderyd, and Västertorp Elis Pettersson, of the Alvik School for hard-of-hearing children, helpfully measured the noise levels of the Stockholm well-baby clinics and the Lekotek as well as the acoustic components of the sound sources used in the main investigation.

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The development of the BOEL attention screening test, representing the application in practice of my conclusions, is the result of the joint efforts of many skillful hands. Signe Ohlsson, B.A., at that time WBC nurse helped me with the preceding trials I especially want to thank Ola Edberg for his constructive ideas and wonderful preparedness to give all practical help regarding the BOEL equipment in different details.

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The photography work has always been a delicate task in a study of infants and children like this one, requiring patience and great skill. Sten Didrik Bellander has always been prepared to sacrifice time for the BOEL project. We have worked well together for many years and his skillful camera-work has helped immensely I want to express my warm gratitude to him as well as to his wife Elsie Bellander who assisted me helpfully by going through my English translation Ingrid Neuteboom has also been extremely helpful by photographing whenever needed, for which I thank her cordially I am further grateful to Hunter Mabon, Stockholm University and his wife for looking through my manuscript from an English viewpoint.

When my study was to be terminated I was lucky enough to get in touch with one of the WBC nurses who had practised the BOEL test for one year She was willing and able to participate in the final editorial and typing work. Thus, Kerstl Söderström gave me the necessary and valuable help without which I could not have accomplished the book. I highly appreciate her loyality and I take the opportunity to extend my thanks to all the staff of Lekoteket på Blockhusudden

The first reproduction of the preliminary results was made possible by the efficient and unselfish work of Ake Tobeck who subsequently helped me with his excellent knowledge. I also wish to express my appreciation to my old friend N O Mauritzon, whose staff and assistants Sven Gustafsson, Harry Lundberg, Peter Mauritzon, Peter Niemetz and Sven Nilsson did a rapid and efficient printing job including the drawings of the graphs

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I am very grateful for the interest in this connection, shown by the family minister Camilla Odhnoff, director Seved Apelqvist, M.D.,

INTRODUCTION

What does communication mean in young infants?

Communication may be identified as information, transmitted to and from one or more individuals by signals of some kind. Information Shannon defines as essentially choice, the narrowing down of alternatives

There is reason for maintaining that the baby from his very first day of life, is involved in continual communication with his environment, provided that the sending and the receiving parts of the communication system are intact. When he cries and someone comes to see what has happened, we may talk of an elementary human communication. Thus, the cry is the information, transmitted by an acoustic signal, which has been decoded and given rise to an action.

If this someone for some reason is unable to hear and/or interpret the baby's signal due to some disability for instance deafness, communication cannot be established by means of normal channels. Evidently then, there cannot exist normal communication when the child for some reason is unable to receive and/or interpret the signals coming from his surroundings.

There are other definitions of communication available but the following study uses the concept defined as the exchange of decoded information according to e.g. Fant[83] Malmberg[116] Miller[124] etc. The information may be transmitted by any sensory activity—visual, auditive, tactile—but the claim for reciprocity can never be refused.

The child depends on communication for his future life as a human being. The preconditions for communication should therefore, be given a central position in the general health check-ups of infants

Communicative development calls for a normal speech and language function. However it is still not explained how children learn to speak as far as it concerns the communicative aspect of speech.

Communicative behavior matures in the normal child, the more information-carrying signals arrive from the environment and give rise to responding activities. The signals have to be detected, discriminated, and recognized, cf Bench[11] in order to form successively growing agents in the service of language formation.

) as quoted by Nesser[130]

d) What stimulus and technique should be applied in screening tests to get useful information regarding selective attention in infants?

The work was disposed in 8 items to answer these questions. Methods, study material, and results with discussion will refer to these 8 items It will be noted *within brackets to what item the part* belongs

[1] Prior to the investigation, studies of available literature gave contingent suggestions regarding current methods of examinations of small children by sound stimulation. Furthermore, behavior pattern at manifest attention, general development norms, and theories on speech, communication, and language formation were previously studied, pp P·1—28

[2] *The knowledge thus gained from the* literature was utilized in an explorative minor study with the aim of finding out if established methods would be usable in practice. The study was undertaken at an infant home Klingsta Spädbarnshem, in a Stockholm suburb, Danderyd, and included 26 babies, aged 1—10 months, pp M.3—4

[3] As a consequence a pilot study was *made at well-baby clinics in Stockholm* using a modification of the methods. The viewpoint was to practise these methods for explorative sound attention examinations with regard to the adaptability for mass screening in infancy This pilot study included 134 infants, aged 2—14 months, pp M.4—9

[4] The conclusions of the pilot study gave rise to the main investigation. The age level in infancy most suited for test ing of selective sound attention was decided. The response percentage was compared with the suitability in prac tice of different sound sources within the frame of society's child welfare program. Finally the study subjects were divided into groups of boys and girls, and the results regarding response percentage were compared. The main investigation comprised 480 babies, aged 2½—13 months.

[5] *Any mass-screening of selective attention* in infants—to be optimally effective—should include sound stimuli which cannot be perceived by children with such hearing defects which impede a spontaneous language acquisition. The residual hearing, often present although the hearing defect may be regarded as severe, allows acoustic components to be perceivable even at comparatively low intensity levels This is true for many types of percussion sounds traditionally used in informal hearing measurements. Therefore the applied sound sources were submitted to a clinical calibration with regard to their audibility for hard-of-hearing children. For that purpose the assistance *of pupils at the* Alvik School, an elementary school and gymnasium for hard-of-hearing pupils in Stock holm, was requested. This first clinical calibration study included 60 school-*children, aged 7—16 years.*

[6] The hypothesis that selective attention is needed for normal speech development called for a follow-up of communicative behavior and speech. Two

years after the main infant investigation this follow-up was undertaken comprising 87 children, aged >2 years —<4 years.

[7] Since a general health check-up for children, 4 years of age, had been proposed by the legislators of Sweden's parliament to be recommended to the child welfare program, plans were made to complete the main investigation of 480 babies [4] by following their development at the 4 years of age level. It had been decided, in 1967 that the Board of Social Welfare should draw up the outlines for this program. Therefore it was hoped for reports from the so called "4-years-of-age check up" to be utilized through a follow-up in 1969—1970. In the first place because of shortage of medical staff, however the "4-years-of-age check up" has not been performed in the Stockholm well-baby clinics to the extent originally intended. For that reason only a minor amount of the examined children could be followed up through the "4-years-of-age check up" as a completion of the first follow up namely 51 children, aged >4—<6 years.

[8] As a proposition for the future the study suggests an application in practice of the results and the methodology conclusions. The BOEL attention screening test is presented as an easily administered method, intended for the general routine of well-baby clinics and other child welfare programs. Since test equipment and presentation technique was meant to be handled by one person, a minor trial testing at Stockholm suburban well-baby clinics preceded the construction. It was undertaken by the investigator and/or a WBC nurse and comprised 26 infants, aged 5—10½ months.

A second clinical calibration had to be made regarding the newly constructed sound sources for the BOEL attention screening test equipment. This was done with the assistance of 72 hard-of-hearing Stockholm pupils, aged 7—18 years.

As a trial the BOEL attention screening has been introduced since January 1971 to all well-baby clinics in central Stockholm and some in the County of Stockholm. The screening is applied by the nurses as a voluntary commitment, and participation is voluntary on the part of the parents as well. The study presents the program only as a tentative experiment with no final scientific analysis.

PREVIOUS STUDIES AND FINDINGS REGARDING COMMUNICATIVE BEHAVIOR, DISORDERS, AND DIAGNOSTIC METHODS

"Learning to communicate" Hardy[60] says, "is the most difficult and rewarding part of growing up ... and everything we do with the young child helps or hinders his ability to understand and be understood by his fellow human beings of all ages." This means a manifold challenge to the pediatrician, the educator and the child psychologist.

Communication as a subject for research covers a wide-spread area, ranging from the field of information theory, philosophy and sociology to linguistics, phonetics, biology, speech pathology, technical audiology and medical psychology. A progressive study of communication in infants and its disorders thus calls for an interdisciplinary teamwork between medical, pedagogical, psychological, linguistic and technical representatives. The delimitations have largely been determined by pure tradition or chance, even though communicative disorders have mostly been dealt with from the starting point of hearing defects.

Early auditory testing

Therefore and because of the call for perspicuity it has been felt natural to survey previous studies by taking an inventory of some audiology findings as the point of departure.

The audiology literature describes what type of behavior might be expected in the small baby at sound stimulation in early testing, e.g.[2, 28, 32, 42, 44, 45, 48, 51, 58, 61, 62, 63, 65, 66, 127, 128, 129, 130, 132, 168, 169, 171] Compared and related to available norms from the infant and child psychology this gives a usable view point for the design of a study regarding the auditory aspects of selective attention.

The majority of investigators distinguish between formal and informal hearing tests. In the formal tests the measurement is controllably standardized, thus providing a basis for threshold determinations and later audiograms. To the present study informal tests are of greater interest.

As early as in the second half of the nineteenth century investigators were convinced not only that newly borns could hear from a physiological point of view, but that the unborn child could react to certain auditory stimuli already in the womb.

The auro-palpebral reflex, one result of which is that the eyes are quickly

shut tight" has been studied by a number of investigators both in neonates and in infants using different sound sources such as tuning forks, whistles, cowbells and pure tone audiometers

On observing the auro-palpebral reflex as well as the general "muscle alarm state pupil dilation and changes in the heart activity it was thought that considerable evidence had been obtained for the audiometric determination of the hearing extent[e.g. 3, 33, 70, 83, 94, 111]

Downs and Sterritt[16] propose a screening method for neonate testing. Two light portable instruments are developed and standardized. one, a filtered narrow band of white noise peaking at 3 000 Hz, and the other a single signal generator producing a 3 000 Hz tone that is warbled, presented with optional outputs of 80—100 dB sound pressure level, measured 10 inches from the sound source The classic newborn infant responses above are recorded.

It has been found that a form of undifferentiated orientation in the general direction of a sound source might be prevalent already at the age of some weeks in a baby lying on his back. It is, in the first place the voice of the mother or of another person replacing her which causes this response behavior Percussion sounds have also been used for testing this response behavior cf[e.g. 131]

Ewing and Ewing[52] have a traditionally important place in informal testing. Their study of 91 children between 0—5 years of age describes the types of sound which normal children usually notice and like Then it tells how they respond to sounds in which they are interested, and the types of sounds which they appear to ignore Tone-audiometry was regarded as inapplicable to the majority of children younger than about 5 years. After the age of 3 months calm and low" voices gave easier responses than percussion sounds which aroused reflex behavior At 6 months, the ability to localize and distinguish between different calm sounds was considered to develop

Bordley Hardy and Hardy[20] modified the Ewings methods in a screening test. They found preliminarily that about 8% of children aged between 4 and 12 months did not respond normally

Di Carlo and Bradley[44] presented a "simplified hearing test for children between 10 months and 3 years. The sound sources consisted of differently combined loud-speakers, comprising undifferentiated noises and music. A localization technique was used in a soundproof room. The weakest sound arousing response was related directly to the hearing threshold level, although no subject responded to the minimum level. Music had a calming influence on infants with behavioral disturbances or other damage to the central nervous system. Those with hearing impairment showed attention but were unable to localize the sound sources.

Dougherty and Cohen[45] informally tested children 4—28 weeks old, using rattles, rustling of paper and the sound of a spoon scraping against the inside of a mug. The sounds were calibrated into high, medium and low frequency levels, and suitable response patterns were described for different age levels.

Eisenberg, Griffin and Coursin[48] used four calibrated noise signals approximately adjusted to the level of 65 dB and 4 000—4,500 Hz. They studied "auditory

behavior in 170 children varying in age from 34 to 42 gestational weeks and from 3 to over 200 hours after birth The aim was to assess the effects of different sound sources on conditions ranging from deep sleep to arousal and alertness.

Goldstein, Kendall and Arick[67] used electroencephalographic audiometry to study abnormal children. The changes in registrations during sleep when pure tone stimuli were presented, were studied in 34 infants, aged 9—59 months The infants were separated into three groups. peripheral hearing loss, a combination of hearing and central impairments, and central perceptual damage. The registrations tended to increase with increasing age the latent period became shorter and the K-complex appeared more often as a possible response pattern.

Hardy and Bordley[81, 82] were advocates of the psycho-galvanic-skin-resistance audiometry in the 1950s This so-called objective method was to be applicable to the differential diagnosis of dysphasia and amentia. Their argument that it is possible to apply it at a much lower age than other methods is, however given more critical consideration now than during the early days of PGSR-audiometry

The fact that the youngest child who responded was 4 months old, and that skin-resistance responses were obtained for three weeks old children, fails to provide the information about how many babies give no response because of e.g. weakened pain reactions and/or no sound attention, and how many because of a peripheral physiological hearing defect. It should be observed that brain impairment and/or mental retardation in many cases is connected with a slower general reaction (cf Luria[111] Goldstein[64]) and deviating perception even regarding tactile stimulation.

The question of inhibited pain reactions respectively fear in normal" infants, impeding the examination procedure, has become central during the years which have passed since PGSR audiometry was first introduced.

Miller Schwemitz and Goetzinger[128] studied the response manner in infants aged between 3 and 5 months at the sounds of paper-rustling, rattles and "snapping sounds" No differences were obtained as a result of sex or race The percentage of positive responses were a function of age Up to 4 months the response frequency was 33% increasing to about 80% at 5 months. The subjects consisted of 54 infants

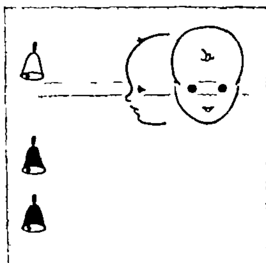
Murphy[131] describes how the first signs of brain functioning connected with hearing can be observed 6—8 weeks after birth. Then the reflex response is reduced and becomes "calmer More conscious reactions begin to develop

Murphy's opinion of different maturity stages in the infant's localization ability has served as a guidance for the present study (fig P·1)

He has the following general aspects on hearing and sound attention. Hearing is defined as the detection of sound by the ear and its transmission to the primary auditory area of the cortex. This definition distinguishes it from reflex reaction to sound and also from listening. — — —

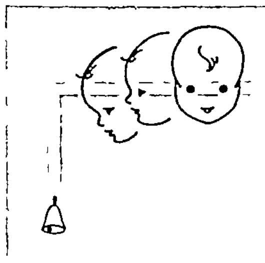
Listening, a psycho-physical process, may be described as the process of paying attention to heard sounds with the object of interpreting their significance. While hearing is fundamental to listening,

Stage 1



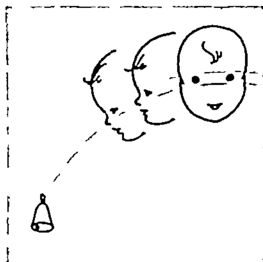
Pure horizontal movement in the general direction of the sound source (≤ 6 weeks)

Stage 2



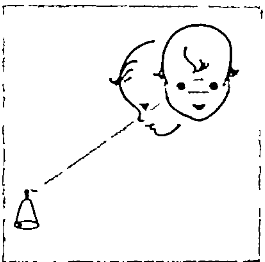
At 22 weeks horizontal and vertical movement commences in localizing sound below the ear

Stage 3



At 28 weeks arc movements commence in localizing sound below the ear

Stage 4



At 32 weeks diagonal movement commences in localizing sound below the ear

Fig P-1 *Murphy's[26] description of head movements in localizing sound to the lower right quadrant.* In 60 % of test cases the localization to the right in each case develops before the corresponding activity to the left. In all cases the downward localization develops before the corresponding upward localization: i.e. stage 3 in downward localization is usually accompanied by stage 2 in upward localization.

numerous other factors can obviously play their part in reducing the ability to attend or to interpret It is essential, therefore, to ensure that reduced skills in listening ability do not lead to faulty diagnosis of severe hearing defect.

Similarly it is possible to illustrate both in the foetus and in the newborn that reflex reaction to audiogenic stimuli is present. However auditory reflex in the very young only involves the basal neural pathways, so that it is possible for a quite severely deaf infant to jump for auditory stimuli and a month or two later to show no response to any but the louder sounds. — — —

By definition we cannot assume that hearing is present until we can demonstrate that there is a cortical function. — — — Cortical function in reference to auditory stimuli first manifests itself as a form of selective inhibition of startle. — — —

Murphy describes the baby's ability to localize sound during the period from 16 to 36 weeks. The response consists of a glance being directed towards the sound source, with head-turning being the next step to follow The author maintains that head-turnings to the right come earlier than to the left.

Speech development stages which may suggest that a child has hearing defect are discussed, one example being that the interest in vocalization and articulation begins to decrease for deaf children at the age of 36 weeks.

Schroeder and Reike[147] discuss the advantages and disadvantages of subjective and objective audiometric methods in the formal early auditory testing. They used conditioning to illuminated toys, a subjective method. When presented to a sound stimulus the child was able to see a toy illuminated by manipulating the loudspeaker equipment to the right or to the left.

As opposed to the objective PGSR audiometry this subjective method may be classified as positive conditioning, i.e rewards for a performance. Toys and pictures were varied after each stimulus presentation, and the conditioned orientation reflex COR, was regarded as being present when a latent period of 1 second between stimulus and reaction was established. Children less than one year old had an error frequency of about 50% The method was thought to be most applicable for children aged over three.

Taylor[164] describes recording of EEG during sleep as particularly suitable when hearing problems are difficult to diagnose. For "peripherally deaf children a very high correlation between responses in sleeping and waking conditions were shown. Children with no hearing impairment but language difficulties responded to very quiet sounds. EEG-methods have been using formal as well as informal auditory stimulation[43]

Taylor[165] has provided practical proposals for this present study He utilizes Ewing and Ewing's[42] division of test types into the three categories of distraction criteria, cooperation criteria and performance criteria. Primarily the distraction criterion has aroused interest It appears to involve the very integration and organization of sense impressions, hypothetically called for by selective attention.

Taylor's technique involves that the infant is distracted visually from the

front by some attractive object, while the tester presents the sound stimuli first from one side then from the other at an angle from the rear Taylor recommends the distraction test clinically around the time when the infant has the maturity to sit upright in a steady position with head and back control more or less stable.

The method of examination applied by Taylor was used as a basis for the explorative minor study conducted during the planning and methodological development reported on pp M.3 It appeared to call for an assistant to the tester

Walden[169] presents the testing of very small children with the aid of baby cries The cries of a 6 months old infant have been recorded and presented to 60 children aged between 1 month and 3 years, and 125 children aged between 1 and 24 months. The method was compared for both groups with pure tone audiometry The results showed the advantages of the baby cries Lower thresholds were obtained throughout for baby cries, and pure tone tests failed to provide reproducible results for children less than 2 years of age The response criteria was of particular interest to this study Head-turning was the usual pattern after 5 months, and reliable thresholds were obtained at the age of 7 months

Sheridan's Stycar Hearing Test[148] has been practically used in this study Its aim is to provide for reliable information about the child's capacity to hear with comprehension in everyday situations (p 3) The choice of sound sources should be based on the child's reaction to well-known, common sounds, especially living speech sounds.

There are children with poor auditory discrimination and gross speech defects (p 4) whose audiograms are quite normal says Sheridan. Other children with hearing loss for pure tones may function excellently as to comprehension.

A test should, in the first place inform about the child's ability to perceive and use spoken language Thus, it is meaningless to apply formal tests e.g. sounds from tuning forks, pure tone audiometers or calibrated whistles when dealing with e.g. mentally handicapped children.

Sheridan makes the usual, and basic, distinction between hearing tests

1 Screening devices" which primarily function to weed out children whose hearing and language are below average in as quick and effective a manner as possible. Further specialist examinations are necessary
2 "Diagnostic procedures" which in a more detailed fashion attempt to define the nature and range of the inability to hear and speak.

Speech, language and hearing are not dealt with from the psycholinguistic point of view but from the medical. Hearing is defined in physiological terms in the same way as by the majority of the investigators referred to viz hearing acuteness for sounds within the frequency and intensity area, relevant for speech learning.

Everyday sounds which form the fundamental material for comprehension of speech sounds contain noise, musical sounds and speech series which are phonetically extremely complex and consist of a basic tone with numerous overtones.

Most "natural" sounds have components ranging over many octaves. Thus, speech covers a frequency area of about

8 octaves from a few cycles (Sheridan mentions approximately 64 Hz) to about 10,000 Hz, assuming that all of our soundproducing resources are utilized. Sheridan states that the upper limit for ordinarily used speech sounds is 8 192 Hz, 5 octaves above middle C expressed in musical terms. Musical tones and natural sounds are normally perceived at least at a couple of octaves above and below the area of speech sounds

Sheridan maintains that the test material should have contents simple enough to be easily understood by the infants. The tester should have a detailed insight into how the test functions for normal children, as well as the general behavior in children to sound stimulation. The test situation should in order to provide an acceptable reference basis, be adapted as exactly as possible to the degree of understanding and experience which a normal child of the actual age possesses, applying development psychology criteria.

The tester should sit in front of the mother and the child. As the sound sources must not be seen by the child, they have to be manipulated from behind by an assistant. Any more or less quiet room is acceptable for testing. The test material is similar to objects in the home and can easily be changed.

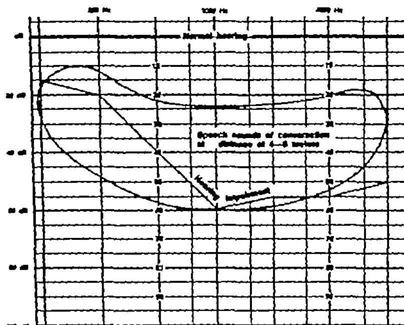
It is impossible to correlate the child's physiological hearing when measured in decibel and/or Herz, with the ability of the child to perceive and interpret speech in a normal room, Sheridan says clearly Each voice and each room will give different results

Even in a quiet examination room, background noise has seldom less intensity than 15—20 dB and often considerably more, see fig M.5

Sheridan points out that the distance hearing of infants does not function at the level of 2.5 years. Many normal children less than 2.5 years of age and mentally retarded children up to the age of 7 or 8 years, appear to have an extremely limited ability to retain contact with a tester not only in time but also in space It is often impossible to catch their attention at a distance of 3 meters for a period sufficiently long to complete the Stycar test, even if the child has normal hearing.

For this reason, Sheridan's tests are only applied at close quarters for children less than 14 months the distance being varied from 50 cm at 6 months to 1 m at 9 months etc. The importance of stating the distance for each individual test is stressed.

In the present study Sheridan's experience of adaptable closeness has been utilized. Sheridan's views on the simplicity of testing infants aged between 9 and 12 months does not entirely agree with the experiences of the present study She states: At this stage of development the child is eagerly seeking through vision, hearing and manipulating, to explore and find meaning in the world around him. He has already learned to associate certain sounds with human beings and the interesting events they initiate, but his experience is still so incomplete and his ability to discriminate between foreground and background noise so rudimentary that he cannot yet take the significance of any sound within his area of attention for granted, but is impelled to support his uncertain powers



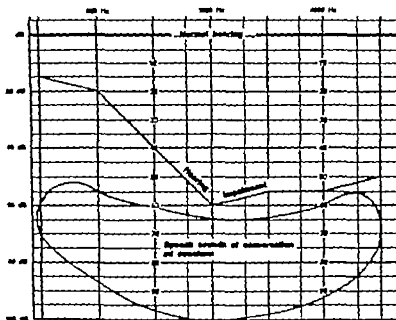


Fig P· The increasing of "auditory strength for the area of speech sounds at decreasing distance All sounds, either they consist of pure tones, lacking over-tones, or they are complex as e.g. every day sounds are transmitted in the space with an intensity which decreases with increasing distance. Thus, it is evident that the distance to sound is important at testing. Even though frequency intensity and duration are affected in somewhat different ways, the distance has to be considered both at hearing measurements, sound attention tests, and auditory training for speech development (from Barr and Stensland Junker[*]).

of auditory recognition and localization with visual verification. (p 11)

"Hence his response to a meaningful sound in the environment is to turn immediately to look for the person or object originating it. This localizing reaction probably plays a necessary part in the child's stereoscopic and stereophonic learning and thus in the formation of his concept of space and possibly of time.

Sheridan's test cannot be applied to Swedish conditions in its original form, but for infants less than 14 months. Wordlists for speaking and whispering are based on phonetic principles of the English language.

Hardy et al.[76] point out that neonatal auditory screening has proved most unrewarding (p 1234) after a study of 4 000 children utilizing a 65—70 dB stimulus, and recommend testing of high-risk infants at 3—4 months of age For the present study the conclusion drawn is that attention screening probably cannot be performed at a lowerer age limit than 4 months.

Non-existent responses to sound stimuli in infants include impairments denoted as aphasia, autism and mental deviations, ranging from complete apathy on sound stimulation to manifested errors of interpretation. There has to date been little success in developing objective measurement techniques for reliable analysis of this phenomenon, Hardy stresses[76] Formal hearing thresholds are of little relevance for such disturbances Other methods of diagnosis and/or forecasting must be attempted

It appears, from audiology findings so far that children with lacking interest in sound still are the clinical riddles The total attention pattern of, for instance childhood autism is mystifying and elusive. It deceives both parents and doctors, and children have been wrongly diagnosed as severely hearing impaired.

The "orientation reflex" respectively the attention response

Different investigators do not always mean the same thing in saying orientation reflex The orientation reflex has an unchanging neurophysiological nature, irrespective of the sense organ stimulated. The effectors of a normal individual orient towards the signal of a receptor stimulus, unless it is of such an intensity or nature that a startle or a flight response arouses [5, 24, 33, 57, 72] If the same signal is repeated many times, the response is gradually extinguished.

Luria[111] gives the example of an animal lying in a resting position when a sound is suddenly distinguished from a wall of indifferent background noises. The animal lifts his head quickly pricks up his ears pays attention and turns his head and eyes in the direction of the new sound, provided that he has an intact hearing. He may take further steps in order to explore the origin of the sound, but if the same signal is reiterated a new association path will be developed which means no measure to be taken

Luria[111] has devoted considerable work to the orientation reflex He points out that significant deviations are prevalent in the reflex activity of mentally retarded children. The naturally conditioned reflexes develop more slowly than for normal children, and it is extremely difficult, sometimes impossible, to develop artificially conditioned re

flexes This effects their speech acquisition in an unfavorable way The necessary level of preparedness for stimuli is absent as well as the necessary intensity of the inhibiting processes. Powerful stimuli may produce inhibiting functions and, conversely weak stimuli may have an unexpectedly powerful effect.

The orientation reflex is not only remarkably less developed in the mentally retarded, but also extinguished more quickly This ought to mean that the mentally retarded child should not have the same selective attention behavior when presented to sound as normal children. It seems plausible that no orienting response arises to weak or even fairly strong stimuli.

Studies of normal children have shown that basic discriminations can be performed at the age of 2—3 months and that children of 3—4 months can distinguish between 2 musical tones separated by one octave. Infants with development disturbances even of a minor nature cannot make this selection before a considerably higher age level. In the case of grave mental retardation, a simple discrimination e.g. between two tones is extremely difficult even for the infant of 8—9 months, according to Luria.

Conditioned orientation reflexes COR, can be quickly formed for infants 6—12 months of age, according to Karlova[100] A well-developed COR can be stabilized for several days, although it is quickly extinguished. This, however takes place more slowly than the time required to build it up Distinctive individual differences could be observed during the formation and extinguishing of COR.

Sokolov's[151] concepts of a neuronal model illustrate general principles for the development and functions of the central nervous system. Sokolov states that the "orientation reflex is unspecific and can be triggered by any increase reduction or qualitative change in a stimulus, irrespective of the sense modality with which the stimulus is connected Two different forms may be observed. one general and one local orientation reflex" During the course of repeated stimulus presentation the generalized orientation response, involving a differential system of analysis is transformed into a localized form, involving activation of the specific analyzing function intended by the stimulus

A registration made concurrently of EEG from occipital and motor regions and PGSR-measurements, including muscle tension, eye movements and respiration, will at the initial tactile stimulation show that a generalized response has been produced. After 24 presentations the only effect will be a slight depression of the EEG in the motor region. Other response components are extinguished.

Goldstein[44] maintains that if a child has sustained damage to the "primary auditive projection system he cannot have an impulse transmission sufficiently fast to be able to commence the complex chain of activities leading to the most suitable cortical integration of the auditive message At an early stage this would be manifested by the non-appearance of the orientation reflex when sound stimuli are presented. At a later stage the result would be the non-appearing, or more or less disturbed language development.

If the damage to the child is innate, his nervous system will most probably adjust to some less perfect function stage, excluding normal speech. Thus, a chaotic reaction will not always arise at auditive stimulation. Externally the child will presumably appear to have aphasia or central auditive imperception with other labels, says Goldstein.

Child development experiences regarding sensory stimulation and psychomotor maturity processes

Although the receptive organs are sufficiently developed at birth to receive all sensory stimuli, they are not adjusted to them from the very beginning. Charlotte Bühler[26,27,28] stresses.

Extremely weak stimuli produce scarcely any reaction at all from the newborn, whereas stronger stimuli, irrespective of their nature, arouse the same type of shock reaction, i.e. a frightened constriction of the body and irradiating movements (cf the auro-palpebral reflex described by e.g. Hahlbrock[74] Wedenberg[171] etc.)

Bühler[28] prefers to classify the movements engaged in the newborn sound reaction with regard to different degrees of violence in the same way as Löwenfeld[113] Being classical their studies belong to this survey

The most violent reaction is. Sudden construction. The eyelids flutter before they are tightly shut whereby the forehead is wrinkled. The muscles of the face are distorted. The lips are pressed tightly together The arms are thrown up in the air and immediately withdrawn back to the body The fingers are stretched out, become clenched and are moved towards the face which they dig into in a cramp-like fashion. The color of the body becomes redder and the body turns away from the direction of the sound. The beginnings of cries are produced. The whole body appears to be maintained in a cramp-like position as if a contraction of all of the muscles had taken place.

The second stage of reaction includes repeated extensions and clenchings of the fingers at the face If they end up at the mouth, the baby sucks them, and the cramp-like attitude is quickly relaxed, even though the state of unpleasentness remains

The third stage represents the mildest reaction. Mouth movements take place, the corners of the mouth turn up, the arms move about, the fingers are extended and clenched, the body is disturbed

Bühler[28] presents an experiment with 5 acoustic stimuli, showing the percentage distribution between these three groups, thus.

Reaction group	Rattle	Whistle	Hand-clapping	Ringing	Bell
1	45	23	18	—	—
2	43	54	54	25	15
3	12	23	28	75	85
Total	100	100	100	100	100

The same groups of movements are involved irrespective of whether the stimulus consists of a shrill whistling, a friendly ringing or a very unpleasant rattling noise.

Löwenfeld[113] performed experiments with babies from the first day of life until the ninth month using as stimuli the sounds from a rattle, whistling, hand and

wood clapping, and "cow bells" 10 babies were tested in each age group with one month's interval. 50% of the new-borns reacted between the third and seventh day of life to all stimuli presented. Towards the end of the first month of life 63% reacted, and towards the end of the second month 78% a figure which did not increase noticeably thereafter

The child of one month still does not react to the quality of the sensory stimulus but rather to its intensity

Although the acoustic stimulus produces an irradiating reaction also during the second month, some differentiation now appears Certain babies manifest, instead of the frightened constrictions and contractions, neutral movements and a clear reaction to tones and noise (Klang und Geräusch) Differentiation as to the quality of the stimulus shows later and is expressed in the duration of the reaction. Average values for a number of acoustical stimuli show that the duration clearly reaches a maximum during the third month.

In the second and third months the quality of the reaction also changes The flight reaction disappears and is replaced by a positive orientation. The child turns his head and also his eyes towards the sound source from the third month. He might be said to become interested" in the sound, since signs of affection" also appear in addition to the development of such an attention response.

Easily recognized pleasure is derived from noise and ringing from the fourth month. The baby laughs, stretches out his hands, babbles, shows affection If the affection curve is compared with reaction duration, an important result is arrived at which is extremely characteristic of human development. the positive affection movements attain their highest percentage proportion later than the longest reaction durations.

Preoccupation with the stimulus has thus begun to become less intensive when joy over the sound stimulus increases Expressed in general terms, as is stressed by Bühler[26,27 28] the easy and comfortable mastery of a situation usually occurs at a time, when the most demanding efforts and the most intensive interest to attain mastery are already over Furthermore *interest in a situation* reaches a maximum at the time when the situation is no longer experienced as primarily presenting difficulties, but when the mastery of the situation is just developing.

It could be summarized, regarding sensory stimulation and psychomotor maturity that acoustical stimulation in the second month still appears to have on the whole an unspecified, partly also negative effect. In the third month the negative effect is neutralized and the reaction duration is now the greatest. In the fourth month the sound stimulus appears to provide pleasure, but interest in it is already decreasing and has been directed towards another sensory field, namely the optical sensory field* [6, 26, 33, 72]

General development norms relevant to selective attention behavior

The limited range of the eye movements at the age of 4 weeks widens successively

) The type of reaction is not described by the author though.

but the wide-angle sight does *not* reach the full stage until late during the pre school age[72] At 8 weeks of age the infant can follow movements with his glance[64] during the second month he is usually able to fixate an object, at 2—3 months he starts to see properly and soon afterwards he is able to follow with his glance an object moved slowly back and forth before his eyes.

Bühler[26] maintains that the baby is able to distinguish an object from its back ground at 5 months and shift attention between 2 objects at the age of 6 months. At 8—10 months he becomes interest ed in red and orange colors[65]

Successively the reflexive grasping from birth disappears and about 16 weeks of age the baby starts gripping an object, for instance a rattle[64] After about 28 weeks the activities of the hand are entirely directed outwards, although the baby still uses his eyes better viz anticipates the grasping and putting things into his mouth[64]

At the level of 28 weeks Gesell et al.[61 65] maintain that the infant keeps his trunk upright and the head steady sitting with support, and Ulin[167 168] states that he is able to hold his head up at 12—16 weeks, and to sit with support at about 36 weeks of age Development levels are almost throughout located at a somewhat earlier stage by Gesell than by Ulin whose norms are based on the study of Swedish children. Both refer to the child without distinguishing between the sexes, though.

Development levels have been found to vary considerably from country to country cf Karlberg et al.[illegible] It is reasonable to assume that cultural environmental factors influence the rate of development due to training habits, etc., the conclusion being that there might be circumstances in the care of Swedish infants in general which lead to the inclination to sit later

Language develops in a definite sequence [50, 54, 100] The first activity of the newborn is usually to cry The birth cries however lack content and merely signify that respiration has commenced and that the baby has begun to adjust to the new environment outside the body of the mother The cry develops into a signal during the following 2—3 months.

The infant becomes silent from the age of 12 weeks when someone talks nearby or when music is heard. He also turns his head from one side to the other at sound stimuli. After an additional 2 weeks, the child consciously searches, Bühler[26] for a sound source with head- and eye movements.

Hagberg's [4] development chart regarding the lower limit for head-turning in direction of sounds has been considered when designing this study fig P:3

Language development and the progress of signal symbolization

The development of communication, i.e. children's social sounds and their continuously turning over into language, has not been studied to the same extent in Sweden as in other countries. The newborn-cries consist primarily of vowels. The consonants appear gradually and the nature of the cry changes. The con-

wood clapping, and "cow bells" 10 babies were tested in each age group with one month's interval. 50% of the new borns reacted between the third and seventh day of life to all stimuli presented. Towards the end of the first month of life 63% reacted, and towards the end of the second month 78% a figure which did not increase noticeably thereafter

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Fig P-3 *Hagberg's motor and mental development chart*

Age/mths	Motorics	Fine movements	Mental development	Development reflexes
0 — 1	Reflex behavior with increased flexor tonus and automatism movements	lacking	begins to fixate	Moro, sucking, gripping, walking reflexes positive
1 — 2	Initial head control and co-ordination with eye movements	lacking	begins to smile	positive tonic neck reflex, neonatal reflexes
2 — 3	Good head balance in upright position	lacking	eye and laughter contact with the mother	neonatal reflexes disappear
3 — 4	Supports himself on his arms in ventral position turns his head in the direction of sounds	unrefined grabbing grip which can be relaxed	begins to babble, looks at his hands	
4 — 5	Initial coordination of arm motor functioning and head movements	tries deliberately to grip articles	turns his head in the directions of sounds, wants company	residual neonatal reflexes should arouse suspicion
5 — 6	Turns round, drags himself along, contributes to sitting up	transfers articles from one hand to the other	recognizes the mother responds to sounds	residual neonatal reflexes clearly pathological
6 — 7	Goes on all fours, crawls, leg movements in turns	good hand position but poor finger motor functioning	single syllable, refined babbling da, ba, ka	suggestions of commencing protection reflexes
7 — 8	Crawls on his knees, sits without support	opposition grip with the thumb opposed to the whole of the hand	afraid of strange faces, powerful reactions to sounds	arm protection reflexes to the side
8 — 9	Sits on his own	opposition grip with the thumb opposed to the radial fingers	says baba, dada etc., is able to "clap his hands	fall protection reflexes appear
9 — 10	Gets up, walks alongside furniture, has difficulty in sitting down	commencement of pincer's grip· tears paper	understands single simple words, plays 'peek-a-boo	arm protection reflex for falling backwards as well
10 — 12	Walks with one-hand support, is able to sit down properly	pincer's grip! picks up crums, piles up cans	says meaningful single words: mamma "ilita dir (=mummy look, there)	absence of protection reflex is suspect

sonants formed at the back of the mouth appear first, such as the velar /g/ /k/ /r/ Some time later the child is able to produce the sounds formed in the front of the mouth, e.g. labials /p/ /b/ /m/ Initially the cry represents discomfort, but after 2—3 months comfort cries also appear Lewis[107 108]

Gesell and Amatruda[44] synthesize view points regarding attention response and the development of social sound-production in the following chart.

Key age" 28 weeks

24 weeks		32 weeks
	Language	
Bell-response — turns head towards bell, grunts" whines spontaneous social noises" (vocal-social)	m-m-m-m cries, polysyllabic vowel sounds	monosyllabic vocalizations such as da, ba, ka

Theories about the development and function of language and speech provide a wide range of differing opinions The behaviorists maintain that language development in essence comprises an increasingly complicated structure of responses to stimuli. Lenneberg[105, 106] however suggests that speech and language be innate arrays of aptitude which are developed in a programmed schedule under the influence of settled maturation processes, cf p P 18.

The fundamental difference between human beings and animals seems to be that the former have linguistic symbols and the ability to produce them intentionally Thereby they are able to move outside the limits of time and space whereas animals appear to be restricted to the concrete actual situation in which they find themselves

Darwin[3] has stressed that all human development depends on the unique growth of linguistic ability when he made his fundamental attempts to explain in biological terms why babies cry respectively scream. It is an inexplicable fact that apes are unable to develop an equally complex means of communication as human speech though their organs for the consumption of food are scarcely different from our speech organs.

It is known that chimpanzees expose miming, gestures noises, body positions movements, etc. In a way this is probably an entirely acceptable signal exchange All the same, there is reason to believe that the symbolization of signals called for in human communication is lacking.

Thus, the secret of language appears to be, above all, its symbol function. Its ability to transmit information by means of signs, consisting of language elements expressed by sound series, by writing, or otherwise concerns both the actual and concrete present, as well as features not present.

evant for transmission of information in a particular language.

Lenneberg[104] represents the current direction in modern linguistics, best known through Chomsky[39] and his ideas of the generative grammar He maintains that the most important differ ences between pre-language and non-language development phases derive from changes within the individual and not from environmental need or changes in the access to stimuli. Thus, language is an innate ability programmed genetically for the syntax. During the process of growth and development it attains certain maturation stages when the program for the actual level can be utilized

Four fixed points are related to such behavior which is influenced by matura tion.

(1) the regularity of the sequence in which certain milestones appear corre lated with age and other accompanying events influencing development,

(2) proof that the opportunities for environmental stimulation remain relatively constant during the development process although the child makes different use of these opportunities as he grows older

(3) the appearance of a given type of behavior either complete or partial, be fore it is of any immediate use for the individual,

(4) proof that the clumsy commencement of a type of behavior is not a sign of goal directed training.

Lenneberg has highly directed his interest into e g. hard-of hearing and other who communicatively disordered children. Lenneberg s overview of the rele vant mile-stones in linguistic development is shown below

Age in months	Vocalization and language	Motor development
4	Babbling and gurgling	The head is steady the tonic neck reflex is reduced, ability to sit supported by cushions on three sides
6 — 9	Babbles, produces sounds such as 'ma or da reduplication of sound is common	Sits without support, drags himself up to a standing position, wishes to grasp things with one hand, first thumb-opposition when gripping
1 — 18	A small vocabulary obeys simple instructions and responds to no (=forbiddance)	Stands alone for short periods without supports, crawls, walks sideways holding on to a bar takes some steps when his hand is held by someone completely developed ability to grasp hold tightly and release.

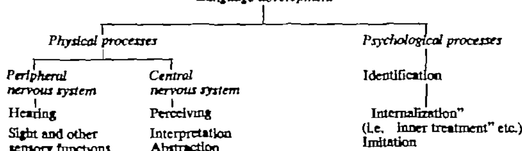
The synchronization of mile-stones for language and motor development is not a logical necessity Certain signs suggest that there is reason to believe that speech development is not a simple consequence of motor development. One specific maturation schedule is special to speech development. The development of children who are different" provides the most convincing evidence for this. This state-

ment of Lenneberg is interesting to compare with the results of this present study as expressed in table R.4 showing a significantly high correlation between performance at attention testing in infancy and e.g. the capacity to change feet in a staircase 2 years later

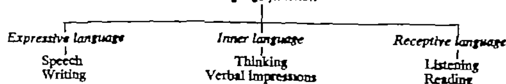
Neisser[136] does not wholly agree with the opinion stated by e.g. Chomsky[30] regarding the cognitive brain function as being analogous to a computor directed process not involving individual choice of attention focus, but for a strict binary program. He maintains that human beings behave very differently and are by no means neutral or passive towards the incoming information. Instead, they select some parts for attention at the expense of others, recording and reformulating them in complex ways. (p 7)

Neisser's opinion offers arguments for the early attention test. there are also 'preattentive processes wholistic operations which form the units to which attention may then be directed and which can directly control simple motor behavior The act of attention itself is better thought of as 'constructive than as analytic primarily because the mechanisms of imagination are continuous with those of perception. (p 86)

Myklebust[132] became an innovator in the field of systematization of language development and types of auditory disorders, disturbing the child's communication, in the early fifties One of his charts is shown below



The symbol function is not limited to words or written language. Other examples are the non-verbal symbolization of music and folklore. Myklebust maintains that symbolic behavior is a more comprehensive concept than linguistic behavior The language function is described in the following way



Inner language might be the basis of symbolic behavior and, therefore the fundament of human behavior It is obvious, clinically that the children do not understand what is said to them be fore acquiring a minimum of "inner language

Bruner*3 describes the early communicative development thus. It is after the infant has abandoned the reflex pattern of response and after a period of diffuse athetoid activity that the directed voluntary activity begins. — — — There is an invariant sequence activation, reach capture, retrieval to the mouth and mouthing. (p 38) Bruner's approach has been useful for the present investigation as he presents a systematic study of psychomotor functions as predisposing the infant to the uniquely human form of language His experiment on infant s psychomotor pattern against the neural background of consciousness has formed arguments for the consideration of age limits in attention testing.

Bruner draws a distinction between doing behavior addressed toward "things" and "communicating behavior directed toward persons Communicative behavior without counter part in doing behavior are for instance eye-to-eye contact—a major link between guardian and infant— smiling, crying, and vocalization.

Bruner refers to communicative growth as a process of conditioning, even though he uses the term code hearing A code of mutual expectancy appears to be established very quickly between infant and parent, when the adult responds to an initiative on the part of the child thus converting some feature of the child s spontaneous behavior into a signal

The opposite viewpoint he recognizes thus. We know from a few studies that there either is an innate predisposition to expect reciprocation of some kind to specific gestures, or there is a very quickly aquired expectation of reciprocation in social communication. (p 56)

The channel of language is doubtless dependent on the growth of interaction codes (p 63) But the form of the code must come from sensorimotor skill (p 60) a refinement or extension of human skill as exhibited in the attentional system and the motor system as represented by man's clever hands (p 64)

Bernstein[13] stresses that it is necessary for human communication to have access to a model in the brain concerning future requirements (p 187) i.e something which is not yet, but which is due to be brought about" (p 171) This must mean that the child should show in his psychomotor behavior if he has this anticipatory model-forming ability

Bocca and Calearo[18] maintain that examinations of communicative disorders at the level of the central auditory system should be based upon the evaluation of disorders of pattern formation and integration This ought also to mean that the ability of giving priority to stimuli in a simply structured test situation could give early information regarding predisposition for speech development. The perception of a sound message does not really depend as such upon a choice between single elements rather it depends on a choice between integrated groups as against chance

groupings. The central auditory function consists precisely of the capacity to organize simultaneous or successive elements into a definite pattern. This capacity responds to a fundamental need of the human receptor (p 338)

Vygotsky[178] who has a leading place as a language theoretician, deviates from the behavioristic approach He questions whether there is a genetic basis for an association between word and thought.

The pre-intellectual roots of speech development have long been recognized, according to Vygotsky The babbling cries, even the first words of the child are regarded as quite clear stages in speech development which are not at all connected with the development of thought. Thus, he maintains that non-verbal thought activities appear early in the same way as speech sounds appear "non-intellectually

Piaget [18,1] the pioneer in the field of child language wanted to study the symbol function as a general mechanism for different systems of representation and as an individual mechanism for thought exchange His conviction was that the symbol formation of children does not take place in some form of reduced adult scale Instead the infant thinking forms an ordered whole with its own logic The link combining all specific features of the symbol formation is the egocentricity of the child's thinking. It takes up an intermediate position between two extreme forms—social and autistic thinking.

Social thoughts aim at goals to be found in the brain of the person thinking. They are intelligent, adjusted to reality and attempt to influence it. They may of course, be subject both to truth and error They can be transmitted by means of language. Autistic thoughts are individualistic and obey their own system of laws.

Piaget considers that autism is the original, earliest form of thinking that is known. Logic appears at a relatively late stage. His experimental studies consisted of conversations with children under systematically controlled conditions In egocentric speech the child is uninterested in the partner and does not expect a reply In socialized speech he attempts to achieve an exchange—he begs, orders, threatens confides and asks questions.

Child thinking manifests itself in different forms. imitation, symbolic games and cognitive representation. All three forms develop as a function of the progressive balance between assimilation and accomodation.

Piaget analyzes each development level with regard to adjustment—to oneself and to one's environment. Eg-centric speech as a separate linguistic form is the extremely important genetic link in the transference from vocal to inner speech.

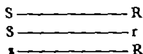
According to the Stern husband-and-wife team[1 162] long since classical regarding language development, the first utterances of the child derive from immediate needs and emotions. The child suddenly discovers that these can be satisfied by linguistic means At a certain stage in mental development, the individual acquires the ability to mean something when he makes sounds, to refer to something objective states Stern [61] who stresses the importance of the logical factor in the process of speech development.

Behavioristic theory respectively cognition through reinforcement and the programming for syntax

Bloomfield[18] maintains that language arises and is developed through repeatedly reinforced stimulus-response activities.

The child vocalizes da hears himself sounding, repeats da the mother arrives perhaps, smiles and lifts up the child, etc. The saying of "da has led to a pleasant result and the procedure begins again The sounds as stimuli are varied for varying responses.

Bloomfield provides a schematic picture of what is taking place as follows. S = the stimulus for the speaker which produces a response = R in the speaker This may consist of r = the medium of speech. Instead of making the direct response R the speaker begins to speak. He applies a so-called linguistic substitute response Thus, a linguistic substitute stimulus = s also appears and finally a response = R may complete the process as illustrated below



The child learns a number of S ——— r s ——— R, eventually producing the result that he does not only understand speech, but he is himself able to use words in the same ways as others

The latter transfer would appear to be the most difficult procedure A gap is often to be found between passive and "active" language There are those who, later in life understand many speech forms but who themselves seldom or never apply these forms in their own speech.

Physiologically speech is composed of a number of nerve activities which are combined into a uniform comprehensive complex of habits, originated by repeated stimulation during the early life of the individual. Bloomfield does not believe in any point-for point correspondence between organs engaged in speech production and cortical centers

Socially important features such as words and their combinations and/or syntax, appear impossible to relate to a point for-point representation in the brain.

Language learning during childhood consists of a training in ignoring differences which are not phonemic in our native language Most difficult is to learn the significant usage of linguistic features which are not significant in our own language.

The method of attempting to produce speech development, primarily in autistic children which is called operant conditioning is based on the classical learning theories of Skinner[149,150] who was convinced that a positive reinforcement in learning through conditioning builds up a stable cognitive behavior even in very low standing organisms. (He pointed out how his experiment-rats evidently acted cognitively because they had formed a cognitive map of earlier learned behavior due to systematic conditioning[149])

In the last few years the operant conditioning as a method, suitable for infantile autism, has been the subject of considerable discussion and hopes. Its basic tenet, conforming to Skinner s theory is to reward the child when he produces speech sounds and to punish him if he does not.

The role assigned to egocentric speech accentuates the completely different interpretation given by a) Vygotsky[176] b) Piaget[140] and c) the traditional behaviorists to the concept of speech development and thinking.

a) Vygotsky s model. speech development moves via social, egocentric speech to inner speech
b) Piaget s model speech development moves from non-verbal, autistic thinking via egocentric thinking and speech to socialized speech and logical thinking.
c) The traditional behaviorists model the development sequence is vocal speech —whispering—inner speech.

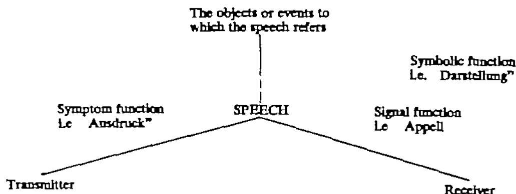
Newman[137] represents an attempt to correlate psychological behaviorism with psychoanalytic methods. Each combined response action requires intercorrelationship in the synapse. At symbol formation there will be a series of combined responses acting together simultaneously producing the same results If one synapse ceases to exist, the other ones remain. The results will be the same as at conditioning.

Menyuk[122] maintains that all syntactical rules guiding the language of adults also generate the language of small children, thus applying Chomsky s[39] model.

Chomsky s[39] grammatical model is analogous to a categorization theory of learning with a triple structure: a phrase structure level a transformation level and a morphological level. A number of rules generate the form of sentences at each level. Chomsky has joined the theories regarding the genetical programming of physiological and psychological functions in organisms. We are genetically programmed for syntax for instance This theory seems to the present investigator to offer an explanation to the evidently syntactical structured gesture language which severely hard-of-hearing children use for their mutual communication.

Karl Bühler[31] analyzed speech as an occurence with 3 basic connecting lines to three different types of reference systems with predetermined innate functions.

The three relations are denoted as: 1) Darstellung relating to the actual content of the speech, subsequently referred to as the *symbolic function* 2) Ausdruck relating to the manner in which the speech is made by the speaker subsequently referred to as the *symptom function* and 3) Appell relating to what the speech is intended to transmit to the listener subsequently referred to as the *signal function* The scheme below shows Bühler's classical model.



Malmberg[116] illuminates Bühler's ideas further- "When the little child cries, the cry expresses discomfort or dissatisfaction. It may be regarded as a *symptom* of the state of the child. At the same time, however it acts as a *signal* to someone in the surroundings which may result in the child being lifted and provided with food A primitive communication system thus arises This elementary symptom or signal function may thereafter instigate a *symbol* function, in that the original sound is associated with a central feature of the situation, in this case hunger The cry may become a symbol for hunger

Theories on perceptual dysfunction due to autism and aphasia

Rimland[145] has specialized in the non-linguistic function and the general behavior of children with infantile autism He hypothesizes that the brain works on an analogy basis, rather than by means of more rigorous analytic processes The perception of objects, situations and problems, thus, give rise to responses as being similar to previously experienced objects situations and problems. This process would mean an overlap in the neurons which are discharged when their sensory representation has been interpreted and transmitted by the memory bank of the brain.

Rimland maintains that the reticular system is the place in the central nervous system where sensory input represented as extremely complicated electrical stimuli patterns, is integrated and transformed into a code The decoding makes the input amenable to the retrieval system, which must be utilized if access is to be had to a wide range of memories

In addition, information transmitted along direct paths is necessary Thus the appropriateness of the coding procedure is the result of a type of triangular process. This should provide us with an approach to the explanation of the phenomena arousal, attention, and habituation

Myklebust and Brutten[125] attempted to throw light upon the perceptual problems of impaired hearing by studying the visual perception of severely hard-of hearing children compared with the visual perception of children with normal hearing. The study utilized tachistoscope technique

Children who were "deaf or had grave hearing impairment interpreted visual stimuli in a manner suggesting a lacking capacity for abstraction. They could not perceive figure against background properly Their visual perception was adequate regarding stimuli which could easily be made concrete From the viewpoint of general perception theory Myklebust's study provides support of the idea that there exist close interrelations between perceptual functions within the organization as a whole, and that the impairment of one perceptual function influences other perceptual functions This functional intercorrelationship is important to the application in practice of results in the present study

Frisina[58] stresses that there is a special group of children which neither audiologists, nor other specialists have been able to comprehend. These children are characterized by a noticeable "distancing from participation in verbal exchanges

with other people They are sometimes called autistic or autistic-like and sometimes mental defectives with personality distortion. The understanding of their hearing mechanisms and auditive behavior is extremely limited.

Aphasia, in addition to autism, is one of the insufficiently researched disturbances, where disorganization and disintegration in the central nervous system is the cause of deficient or non-existent speech development in children.

Junker[67] calls for linguistically independent test methods which can be applied to *aphasic children standardized* for Swedish conditions, recommending Wepman's[173] Language Modalities Test for Aphasia, LMTA, which is constructed *for use both in clinical and research* work.

Since Wepman seems to offer a first, systematizing approach to the organization and integration of neurological functions, assumed to be the basis of language capacity in this study it has been regarded as suitable to finish the present survey by presenting his scheme

Wepman includes in the concept of aphasia disturbances which affect those parts of the brain function which correspond to concept formation, i.e. both symbol formation and language storage He distinguishes between five types of aphasia

1) *Pragmatic aphasia*, which is a disturbance in symbol comprehension whereby incoming signals cannot be associated with adequate concepts.

2) *Semantic aphasia*, which is a disturbance in symbol formulation where the difficulty is to assign a meaningful verbal sign to a previously acquired concept.

3) *Syntactic aphasia* which is a disturbance in symbol formulation manifested in the ability to apply previously acquired knowledge of grammatical structure.

These three types mean a breakdown of three very basic processes in the *language function*.

a) Recognition and identification of an incoming signal by associating it with previously acquired concepts

b) application of a previously acquired verbal symbol to a concept,

c) inclusion of a verbal symbol in a previously acquired and relatively automatic grammatical system.

4) *Jargon aphasia*, which is a disturbance in symbol formulation, where previously acquired phoneme sequencies which have formed comprehensible language units no longer appear meaningful, but are changed into incomprehensible combinations.

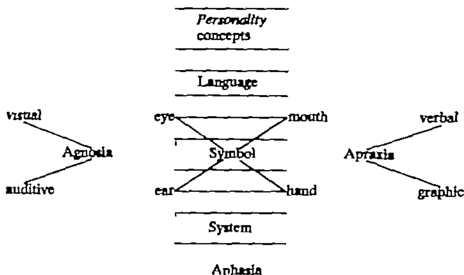
5) *Global aphasia* which is a disturbance in the language function manifested in the inability to make verbal responses to stimuli, or where the responses consist of an automatic word, a phrase or a phoneme sequence.

All of these five types are related to central *integrating language functions In* addition, there are communication disturbances in the language function related to the transmission between the modalities, i.e channels between *incoming and* outgoing language impulses. These disturbances are divided into·

A *Agnosia* meaning the inability to interprete an incoming signal because of transmission defects relating to a specific stimulus modality—which is manifested in the ability to copy and imitate or to identify stimuli, or to match them with identical stimuli.

B *Apraxia*, meaning a disturbance in the ability to transmit or express a motor response along a specific modality—which is manifested in articulation difficulties, writing difficulties and other expressive functions.

Wepman s model of the language function clarifies the above discussion



External conditions potentially influencing the communication of infants

Further environmental influence on the infant s speech development has been investigated in Sweden by Alin Akerman[1] She has described 52 children in Stockholm infant nursery homes by using Griffiths'[69] Mental Development Scales, Lindstam s[110] standardization. She found a somewhat lower value than that of the normalization group (p 47) on the speech and hearing scale. Very small differences were found between children coming from different social backgrounds, though

One could have expected a greater effect on the speech development scale in relation to "social deprivation We are accustomed to count with negative effects of the "collective milieu" However we do not know so far if the average Swedish home milieu is more stimulating than that of a nursery home of today It might be that the current propaganda for early training has influenced the nursery home staff in a positive direction.

The importance of early recognition of the stimulance need is stressed by many authors e g. Bernstein[12] The quality of early verbal stimulation at home or at

nursery schools affects later mental capacity Alin-Akerman maintains that the positive result may be due to the fact that the average caretime has been shorter during the last years (p 47)

The development, *thus, is impeded by* the length of a stay in a nursery home These tendencies are most marked for older children, i.e children older than 6 months, who have stayed longer than three months in a nursery home. — — — This means that the qualitative aspects are very important for the development of the child — — — (p 47)

Also for social emotional development there are lower values "This might be understood in such a way that the children during a certain limited time have the possibility to benefit from stimulance given by the nursing staff whereas a prolonged stay in a nursery home does not give the children sufficient emotional satisfaction (p 48)

The study emphasizes the age between 6 months and one year as being a period in life during which it is important to find out about communicative behavior since the child then seems to be optimally responsive to external conditions and/or stimulation.

A contribution to the study of external influence and/or social deprivation, made from another point of departure is Brackbill's[31] study of the smile responses in infants at home respectively at institutions Extinction of the smile response as a function of a reinforcement schedule was investigated The results showed that the smile response reached its peak earlier for infants at home than for those institutionalized, within a range of 6—8 weeks *for the former and 9—14 weeks* for the latter Response strength also attained an earlier peak for infants at home When this peak is reached, the response strength decreases for both groups and sinks to a low level

Ambrose[3] measured the accumulated duration per half minute of the smile expressed in the smiling time per stimulus presentation and in latent period for the first smile in each presentation. Both of these measures turned out to be sensitive to every change in the internal and external environment of the baby

Speed of smiling and the breadth of the smile showed positive relationship to the length of the smiling period and to each other *Smiling time per presentation* was used as an indication of response intensity Stimulation was standardized, and the measurements showed that smiling time almost always began at a high level and was gradually reduced during the period of stimulus presentation, until the *smile died out or reached a low level. 10* institutionalized infants 13—26 weeks old were studied.

Reingold et al.[144] maintain that infant vocalization receiving social reinforcement was on the average influenced neither during the conditioning nor the extinguishing trials which appears somewhat astonishing, since one form of reinforcement was smiling.

The importance of the smile at infant attention testing has been considered regarding the methodology of this present study

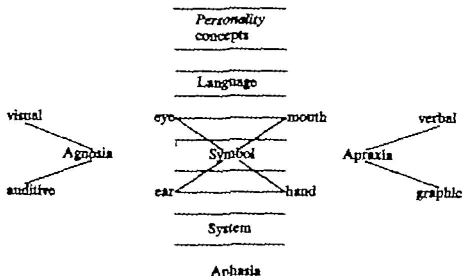
Summarizing considerations

Literature studies have suggested the following considerations with regard to

A *Agnosia* meaning the inability to interprete an incoming signal because of transmission defects relating to a specific stimulus modality—which is manifested in the ability to copy and imitate or to identify stimuli, or to match them with identical stimuli.

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Aphasia

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METHODS

Theoretical considerations

The problem to clarify the influence of selective attention in infancy on consecutive communicative behavior called for the following methodological aspects

Methods for the infant examinations [2] [3] [4] should trace and check the ability to direct attention focus. Preferably they should be mastered within the general routine of the child welfare system.

The attention focusing of a baby can be observed by his searching for some interest arousing signal, although he has been kept attracted by some other signal Stimuli used for this purpose should, in the first place arouse curiosity and excite the baby with a news value*

When dealing with ages under one year it seems reasonable to start with a visual stimulus to attract the initial interest, before the capacity to pay attention to an interesting sound is to be checked. Sight dominates the infant's attention field during the first three quarters period of life* [16,26,33,64] If the baby leaves the first, on principle more attractive visual stimulus in order to search for a second stimulus, the tester should have reason to be certain that he really cares for the second one, i.e. the sound. An initial, firmly established eye contact is an absolute demand, though.

Attention arousing sounds should not only be attractive Their origin must also be kept reliably apart from other stimulation, visual or tactile Even though the wide-angle sight is highly restricted during the first year of life* [8-33,72] the sound sources must be as invisible as possible, and small enough to be kept out of touch, too

If, moreover it be decided that the examination be mastered by one person, the equipment should be able to be handled within arms length's space The infant under one year of age will ignore irrelevant and peripheral sounds, irrespective of their intensity Luria et al.[112] point out. This means that there should be no claim for the soundproof room of an audiology clinic. The environment should be as natural to the infant as possible Comparatively great variations in noise level (cf fig M5) could be regarded as compensated by the gains obtained in a psychologically more favorable milieu.

Methods for the follow-up examinations [6] [7] should aim at catching the essence of childhood communication. At the same time, they should include components, reasonably covering the need for a quantification which made comparisons with the results of the infant examinations possible.

No formal psychologic tests standardized for Swedish infants and small children were available at the time when the children, examined in infancy had reached an age suitable for re-examination. It had been decided that too long time in between should not elapse. It is well known that current baby tests have had low correlations with later testing. Klackenberg-Larsson and Stensson maintain in Karlberg et al.[44] Like most other authors we have found that tests for infants have little long-term predictive value for normal children (p 90) Quoting Bayley's[10] explanation they point at the influence of environment etc.

The meantime of two years for a first re-examination was regarded as suitable. The lack of reference basis from earlier investigations constrained the endeavor to set up comparable items. The experiences of other countries had to be utilized in combination with a tentative series. Therefore, it has to be strongly emphasized that the study is an explorative one.

Regarding the utilization of the 4-years-of-age check-up* the similar reservation has to be stressed. The follow up is tentative.

Methods for statistical representations [4] [6] [7] should not be overdone. Thus the calculations have been highly simplified. The distributions of frequencies regarding the results from the main investigation are presented as percentage positive responses for each age group individually (figs R.1—7). Thus, they should not be falsely interpreted as cumulative frequencies. They could have been shown in the form of histograms. However this type of statistical representation was meant to obscure the relevant information aimed at, although the author is well aware of the age groups being small when it comes to percentage calculations.

The analysis of the intercorrelation between the first examination and the two follow-ups is simple. The material has not been regarded as valid for more than a mere fourfold correlation, since the dichotomization is unequivocal. However some of the dichotomies in the study of the 4-years-of-age check-up have not been regarded as relevant for analysis.

Since the phi coefficient (Φ) is a particular case of the product-moment-correlation coefficient, applicable when both the variables are dichotomized, cf Ferguson[44] pp 106 the choice has been to combine all chi square (χ^2) values with the phi-coefficients, when the results of the main investigation are associated with those of the follow-ups.

The use of the phi coefficient may seem superfluous, but since it adds information to some readers, the decision was to present it. When both variables are evenly divided, viz $p = p_j = q_i = q_j = 0.5$ the Φ has the minimum of —1 0 and the maximum of +1 0. In other cases one but not both these limits may be attained. Since $\Phi = \frac{\chi^2}{N}$ and thus N $\Phi = \chi^2$ one can easily

test the significance of a reported χ^2 value by referring to a chi-square table with 1 degree of freedom.

Practical design: Results of two explorative studies [2] [3] giving methods for the main investigation [4]

The minor study at the infant home Klingsta spädbarnshem [2] and the pilot study at well-baby clinics [3] will first be presented, since their results led to the development of methods for the main investigation. Thus, the figures achieved in these studies have only been used for preparatory considerations regarding methods.

[2] *The minor study*

From a methodology point of view the technique practised at Klingsta [2] might be labelled as "distraction" referring to Taylor[186]. The sound producing objects used belonged to the arsenal of the Child Audiology Department of Karolinska sjukhuset, Stockholm.

Sound sources [2] Small plastic doll bell, scratching of spoon in mug, rustling of tissue paper, wooden whistle and sss sound from behind.

The whistle was not formally calibrated, but clinical experience of hearing examinations had given the approximate values of 85 dB at a distance of 1 meter and a frequency of about 3 000 Hz. (The values may vary slightly due to the strength of whistling.)

The examinations called for the participation of 3 adults. One examinator sat in front of the baby and the other stood behind, producing the sounds. The baby sat in the lap of the nurse. Response criterion was decided to be head-turning in the direction of the sound after attempts to divert the visual attention by means of

Table M 1
Head-turning response at sound stimulation in a minor study of 26 infants at Klingsta spädbarnshem [2].

Age in months and days	No reaction for any sound			Turns head to one side			Turns head to both sides			Subjects in prelim. study		
	♂	♀	Tot.	♂	♀	Tot.	♂	♀	Tot.	♂	♀	All
1.0 — 1.29	3	1	4							3	1	4
2.0 — 2.29	2		4									4
3.0 — 3.29		1	3								1	3
4.0 — 4.29	1		3		1	1				1	3	4
5.0 — 5.29	1		1							1		1
6.0 — 6.29		1	1		1	1	1	1		1	3	4
7.0 — 7.29		1	1				2	1	3	2	2	4
8.0 — 8.29												0
9.0 — 9.29							1	1	[illegible]	1	1	2
All [illegible]	9	8	17	0		2	4	3	7	13	13	26

some attractive tool. The results were not differentiated regarding sound sources.

The table shows that no baby under 4 months of age gave a positive response, which was the lowest age level when 1 girl turned head to one side

[3] *The pilot study*

Following after the minor Klingsta study a pilot study of 134 infants was decided to be located at Stockholm well-baby clinics This called for a principal modification of the methods according to the claim of a technique mastered by one person (and the mother) In the report of Stensland Junker[158] to the University of Stockholm the complete findings are presented (in Swedish)

The choice of well-baby clinics [3] [4] The routines of the well-baby clinics do not, as a rule include examinations extending beyond the general health check ups, mainly because of limited time during the doctor's reception. For several reasons, there was a high number of appointments when the study took place The atmosphere of the waiting rooms was characterized by noise, talk, cries, playing, changing of diapers, etc.

Due to the helpful attitude of the staff the examinations could take place in one of the nurses offices It is probable that this resulted in many cases, in the mother and child regarding the examination as a welcome relief during the waiting period The nurses rooms had a more private character than the waiting room and the clinic room and comparatively undisturbed premises. It was quite possible to conduct the examinations within the framework of the general routine

This was important, since it was thought advisable to utilize the opportunity of conducting the examinations in as uniform an environment as possible. A performance in the children's homes for instance in connection with the nurses visits, would have introduced a milieu factor which might have varied too much.

On principle, the investigation could have been located to a medical clinic, but administrative problems would have arisen risking to make the study impossible. Neither with regard to personnel, nor to other premises, was a clinic in a hospital dimensioned to provide for special studies of several hundred, presumably healthy infants The summonings would have necessitated explanations to the parents which might have worried them and led to complications.

Some parents would perhaps have been unable—or unwilling—to come and it would scarcely have been possible to

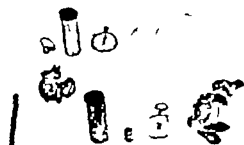


Fig M 1
Stimuli used in pilot study of 134 infants at well-baby clinics [3].
Sound sources (from left to right) "rattle bell, Montessori sand-cylinder stopwatch, "cradle tissue paper
Visual stimuli (line below from left to right) red, short, round stick, red toy rattle, formed as a cock, red- headed" Montessori sand cylinder green thimble, golden mini-music box, soft toy-bird with red flannel nib.

isolate the reasons, or to analyze them in a satisfactory way Bearing in mind that parents take their children to the well baby clinic more or less on their own accord, it was plausible to assume that the majority would have nothing but a positive attitude towards this extra check-up of the health Fig M 1 shows the aids for the examinations, and table M.2 summarizes the findings according to the claims of this present study

Sound sources (fig M.1 and table M.2) comment [3] Sound stimuli were presented in the order in which they are photographed at fig M 1 Thus, the dif fuse clapping noise of the plastic container denoted rattle was always presented first. Thereafter the bell followed concealed in the palm of the hand, then the Montessori sand-cylinder etc. During the final stages of the pilot study it was decided, though, that the order of presentation should be rotated taken into account the possibility that the infants might adapt to the sounds in a way which could not be controlled.

The plastic *rattle* fastened at the top of the middle finger needed only a rapid movement with the finger against the palm in order to sound. The little jingle *bell* was specially constructed to sound at very small hand movements, as there was a little lead pellet rolling freely inside it. First it was fastened to a rubber band, then this was changed to a small silver ring. The bell was turned to the palm, thus being totally hidden, and easy to handle, fig M.2

The infants were not able to notice that the sounds were coming from the hand As a trial, the tester moved the hand,

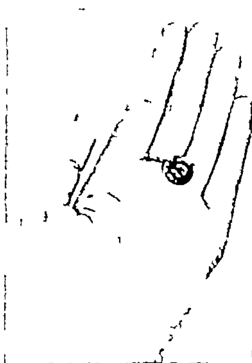


Fig M.2
Little jingle bell found to be the most practical sound source to handl out of the infant's sight nd arousing interest [3] [4].
Photo Karolinska ...

with the source sounding inside it, around the baby's body to find out if this gave some additional information on sound attention behavior of interest for the methods. Many babies followed attentively the movement of the sound, searching" it.

The bell was more convenient than other sound sources. This does not show in the table, neither does it tell to what extent the sound attracted the baby s curiosity and interested him.

The need for the sound sources being invisible to the baby during the test course was easy to achieve also with the *cradle*

[3] *"Conditioning" trials* It appeared

desirable to study whether conditioning could be used as a possible testing technique and if methods developed in audiometry e g. Barr[3] could perhaps be applied to the study of sound attention even though this conditioning — with regard to the strict sense of the word — had to be highly modified.

The *Montessori sand-cylinder* was presented with conditioning requiring the assistance of the mother Before the testing procedure could be settled, 34 infants were subjected to trials

The part of the Montessori sound discrimination material applied consists of wooden cylinders filled with fine sand Babies preference for the red color was utilized, since the cylinder used as visual attraction was red headed

It was necessary however that the infants had attained an age for a firmly established capacity to grasp i.e at least about 5 months (according to Ulin[187 189]), for conditioning with the wooden cylinder to be possible. The trial was limited to children over the age of 6 months.

Thus, the red-"headed" wooden cylinder was shown to the infant who reached out for it, visually stimulated Then it was shaken in front of him so that he could reach it and hear the rattling noise produced

The cylinder was also shaken at a distance of about 20 cm from the infant s ear at the same time as he was being observed and before he could satisfy his desire for tactile stimulation and put the red head into his mouth Shortly afterwards the same sound was presented by means of the other blue headed" cylinder about 20 cm from the baby s ear out of his vision. The mother had to contribute instructed by the tester The cylinder was slipped to her and she shook it without its being seen in the same way as the red variant had been shaken previously fig M 6d.

The *stopwatch* had also to be presented with the help of the mother The stopwatch was switched on the whole examination time, so that the starting click" would not attract the baby s attention too early

The infants were allowed to listen to the stopwatch became interested in the sound, were then distracted by means of some other visual stimulus during which time the watch was slipped to the mother A latent period, sufficiently long for the infant to forget to search for the initially visual stimulus of the stopwatch, elapsed Then the mother held up the stopwatch at an angle from behind the child's ear at a distance of about 20 cm quite outside the range of his vision

In the majority of cases the stopwatch failed to stimulate the interest of the infant in a manner such as to arouse an attention response with head-turning. The method of presentation was, therefore, revised for the main investigation. The presentation, then, was not preceded by the conditioning procedure

In the pilot study responses were defined as positive in the cases where the infants reacted with a head-turning towards the sound source. Negative response meant either that a sound had aroused no attention or that a stimulus had not been presented Fig M 3 summarizes the results

Table M 2

Percentage distribution of positive responses to stimulation from 6 different sounds in a pilot study of 134 infants at Stockholm well-baby clinics [3]

Criterion for final positive responses was head-turning in the direction of more than 2 sounds after initial visual stimulation.

Age in months and days ♂ + ♀ 68 + 66	N 134	Positive responses to sounds as percentage of presentations: Plastic container "rattle"		Small metal bell		Montessori sand-cylinder		Stop watch		Plastic container "cradle"		Thin cellulose "paper"		Final judgement: Absolute frequency of infants			TOTAL N
		+	—	+	—	+	—	+	—	+	—	+	—	+	—	?	N
2 — 2.29		0	100	22	78	0	100	0	100	11	89	0	100	0	9	0	9
3 — 3.29		10	90	0	100	0	100	0	100	0	100	10	90	0	11	0	11
4 — 4.29		26	74	13	87	0	100	13	87	40	60	26	74	3	10	2	15
5 — 5.29		47	53	70	30	6	94	18	82	47	53	47	53	7	10	0	17
6 — 6.29		77	23	70	30	23	77	62	38	46	54	46	54	7	4		13
7 — 7.29		90	10	54	46	63	37	54	46	54	46	73	27	9	2	0	11
8 — 8.29		84	16	84	16	68	32	68	32	68	32	68	32	16	3	0	19
9 — 9.29		84	16	84	16	58	42	58	42	58	42	84	16	14	5	0	19
10 — 10.29		85	15	77	23	62	38	69	31	69	31	85	15	9	4	0	13
11 — 11.29		—		—		—		—		—		—		1	1	0	2
1 — 12.29		—		—		—		—		—		—		3	0	1	4
13 → 13.29		—		—		—		—		—		—		1	0	0	1

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sources could be compared with each other from the viewpoint of practical suitability

Critical viewpoints regarding methods for acoustic stimulation [2] [3]

The two explorative studies led to the following considerations. The much applied spoon-and-mug type of acoustic stimulus, e.g. at screening of hearing acuity is evidently unsuitable for the purpose of the present study to examine selective attention at WBC It is practically impossible to let a spoon scrape within a mug without being seen, if the test is to be carried out by one person alone.

The same limitation is valid for the use of a whistle as well as the techniques calling for the participation of the mother In the latter case, there is also the risk of bias An over-ambitious mother could be so eagerly shaking the sand-cylinder that the child could catch sight of it in the corner of his eye or feel the move ments of the mother s body fig M.6d. While participating in the presentations of the stopwatch there was a risk that the over ambitious mother held it so near the infant s ear that he could touch it.

The main investigation [4]

Visual attention stimuli [4]: After the reduction of the stimuli used in the pilot study fig M 1 according to the ex perience during the examinations [3] the red, short round stick, figs M 6e and M 10 was chosen to catch the attention of the infant. It was found to be most suitable because it was simple to handle and stimulating enough to be attractive The only disadvantage to be experienced was the risk of the infant hurting himself by putting it too rapidly into his mouth.

Sound sources [4] To the stimuli used in the pilot study fig M 1 finally a few more were added. Table M 3 p M 10 gives relevant data of the sound sources. They were all transferred to sonagrams, fig M 8 with a distance from the microphone of 20 cm soundproof room. The sound presentations were rotated regarding their serial order during the examinations of the main investigation. Due to the practical course of presentation the *crushing of two types of paper and plastic* was calculated as one sound. The voice of the tester had been used in the pilot study mainly to infants with non-existent attention responses and is, therefore, not reported in table M.2. It is put in brackets *with the whisper* Whispering has been used throughout the main investigation, concluding the examinations, cf fig M 10 Results are reported for nine sounds in table R.1

Among the added sources the *mini-music box* was applied with a conditioning technique described in detail in figs M 6a—c, M 12. Although this sound source was highly attractive, a disadvantage was that it had to be wound up, which reduced its applicability under hurried conditions.

As the electro-acoustic *pure tone generator* was too big and clumsy fig M 4 it could not be hidden reliably from the infant s sight. No response could be registered as a positive one since it turned out to be impossible to divert the visual attention from the apparatus. More

Table M 3
Description of sound stimuli used in main investigation [4]

Sound pressure level dB re 0.0002 microbar at 20 cm distance	*Sound description*	*Material description and name at protocol card*
35 — 45	Weak, diffuse, rattling sound	Small plastic container with a hard sound producing object inside it, attached to the middle finger called the "*rattle*
45 — 55	Clear "bell-sound"	Little jingle bell, metal, attached to the palm of the hand, with lead pellet rolling freely inside it, called the "*bell*"
30 — 40	High-frequent, melodic, sound	Wooden cylinder containing fine sand, from the Montessori material series for sound discrimination, called the *sand-cylinder*
30 — 40	Ticking	Ordinary stopwatch, called the *stopwatch*"
45 — 55	Loud, rattling noise	Small half-moon shaped plastic container with two lead pellets rolling about inside it, called the "*cradle*"
30 — 40	Soft rustling	Crushing of: *Tissue paper* called "*P*
45 — 55	Ordinary rustling	Crushing of: Firm *cellulose* such as house-hold paper called "*P* (*cellocotton*)
50 — 60	Loud rustling	Crushing of Plastic cloth (not woven) called "*Pl*"
60 — 70	High-frequent, rustling clear tone	Small music box, called the "*mini-music box*
30 — 40	Quiet female voice	The female tester s low voice, called voice
30 — 40	S-sound, such as /ssss/ or the name of the child, or pet name made in a whisper	The tester s whispering voice called "*whisper*"
40 — 90	Pure tones, 3 000 Hz 5 intensity levels from 40 dB to 90 dB	Electro-acoustic generator adaptable to the hand, producing continuous and intermittent pure tones called the *pure tone* or *PT*"
Not measured	Percussion sounds	Different experimental bells etc. called *other sources*

over pure tones did not appear to awaken interest in the infants examined Therefore the generator was solely used as an experimental set-up in the main investigation and in the follow-up figs M.22—23

"*Other sources*" mainly used to non-respondent infants, comprised e g. containers with lead-shots pellets and gravel wooden rattles hand-clapping finger clicking and similar traditionally atten-

tion-awakening noises. Formally they were not regarded as belonging to the experimental series of sounds although reported in table R.1

Completing the description of experiment conditions, it must be mentioned that the sound pressure of the examination rooms—also for the purpose of the follow-up at the Lekotek —was measured with Brüel & Kjaer Sound Level Meter 2203/Octave, filter 1613 fig M.5

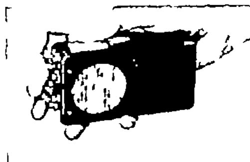


Fig M 4
Pure tone generator applied to the hand producing 3,000 Hz at 5 optional intensity levels intermittently and continuously. The soundability is evident according to the claim for invisibleness.
Figs M.22—23 p M.30 show how it was hidden when used in the follow-up
Photo Karolinska sjukhuset

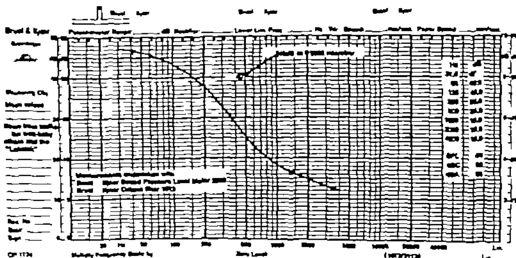


Fig M 5
Average noise level at 5 well-baby clinics in the inner area of Stockholm city and at an office and industry house including a child advisory bureau called Lekotek.



Fig M·6a
"Conditioning" with mini-music box. Two mini-music boxes were used, one sounding by playing a melody the other silent. The playing box was to be switched on and off by a little button. It had to be wound up before the testing.

The infant was shown the box when the melody was playing, he got interested and wanted to grasp it.

Photo Ingrid Nesseboom



Fig M 6b
The tester suddenly switched it off and exchanged the playing box for the silent one which the baby then, was allowed to take and to keep. He examined the silent box and put it into his mouth (normally).



Fig M 6c
After a short latent period, the tester switched on the pl ying box at distance of about 0.5 meter from the ear The infant had been given time enough to get very interested in the silent box when the sound, formerly coming from the box as experienced by the infant, came from somewhere else



Fig M:6d
Principal technique when the mother gi es assistance at conditioning
It is evident that the body movements of the mother may be perceived by the infant, as well as the visual stimulation in the corner of his eye irrespective of the limited wide-angle sight of this age. Here the Montessori sand-cylinder is shaken by the mother



Fig M:6e
The short red round stick was easy to handl and stimulating nough to catch the infant's curiosity and attention.

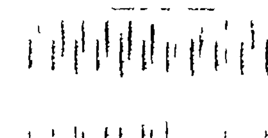


Fig M:6f
The infant leaves the visual attraction f the red stick to search for the bell, usually hidden totally in the hand — here only shown for the purpose of illustration.

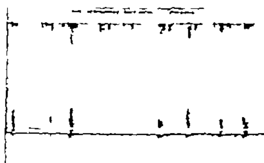


Fig M 7
The sound sources used for conditioning were none f them as handy and small as the little jingle bell. The rattles on the picture are large.

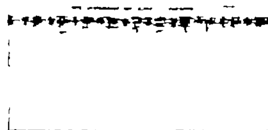
Fig M 8
Sonagraphic description of sound sources chosen for the main investigation of 480 infants at ell-baby clinics [4]
From an acoustic point of view it is easily recognized that the sound of the Montessori sand-cylinder and the crushed tissue paper do not include basic tones within the frequency area of ordinary speech sounds. On the other hand the bell — from a practical point of iew most easily handled and interesting to the baby — has basic sound components coinciding with basic tones in the speech sound area.



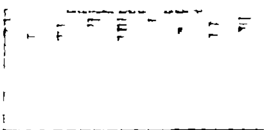
a. Rattle



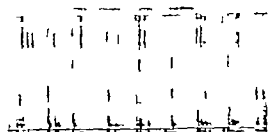
b. Bell — the little jingle bell cf fig M.2



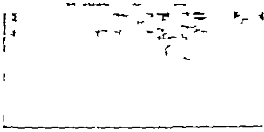
c. Montessori sand-cylinder



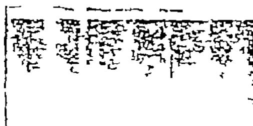
d. Stopwatch



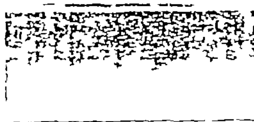
e. Cradle



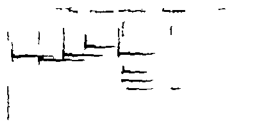
f Tissue paper P



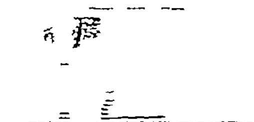
g. "Cellocotton household-paper P



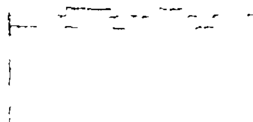
h. Plastic, Pl



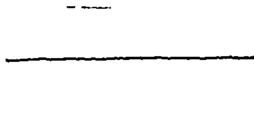
i. Mini-music box



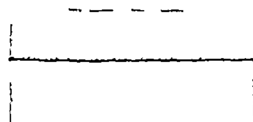
j. Voice [illegible]



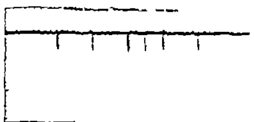
k. Whisper [illegible]



l. Pure tone, continuous, 3,000 Hz



m. Pure tone, intermittent, 3,000 Hz



n. Hand-bell for follow-up, cf fig M..4

Methods of the examinations and reporting system [4]

Anamnesis [4]. When the infant was placed at ease in the lap of the mother or the person bringing him to the well-baby clinic anamnestic data could be obtained, for example weight at birth, sibling order age of father and mother vocational and marital status, pregnancy and delivery etc., cf fig M-9 In the spaces called Status presens notations were made partly regarding actual illnesses or otherwise remarkable conditions, partly regarding the infant's type of cooperation Four classes were applied. Attention, orientation, eye contact, interest, each divided into a positive and a negative evaluation.

The mothers were moreover asked about their impression of the baby's hearing, whether they remembered when he began to fix his glance, when he laughed for the first time, and which types of sounds or commencing word formations were manifested by the infant. A general question was also asked as to whether the infant appeared well developed

The space marked shot on the protocol card, fig M-9 regarded an eventual polio injection given before the examination. Even though it seems unwise to give a shot" deliberately before examining selective attention, it was regarded as interesting to know about the eventual influence of a pain experience preceding the test. Therefore the infants having had shots were not excluded from the investigation, but compared with the other ones.

Own disturbances included breathing through the mouth, crying, noises from the chest, rustling, etc., as well as gurgling noises which might screen the child from external sound impressions, etc. "External disturbances" were only noted to the extent that they had been regarded as forceful enough to distract the child.

It was pointed out to the mothers that participation was optional, the examination being a part of an investigation under the auspices of the Karolinska sjukhuset. The vast majority showed a considerable interest. The reasons for refusing to participate appeared to be shortage of time.

A necessary requirement was that the tester did not know the baby before the examination, in order not to be biased by the previous information, collected by the nurses or the doctors However after noting her own assessments and information obtained from the mother it was extremely worth while for the tester to get a possibility to check with the nurses and the doctors. The nurses were acquainted with the home milieu of the infants and they mostly had had continuous contact with both mother child and the rest of the family After completed examinations the notations were transferred to punch cards for data processing.

Examination [4]. It was regarded as favorable that the first contact be connected with a smile or else some other signs of a positive approach, e g the stretching of the arms towards the tester who sat in front of the mother and the child. When the necessary firm eye contact had been established, the tester had to observe the following functions.

The capacity to fix and hold eye contact,

to watch and follow a movement with the look,
to sit steadily
to grasp and grip
to explore with the mouth,
to orient with stabile head movements in the firm direction of the sound source.

The visual stimulus was shown about 0.4 m in front of the baby's face. To check that the baby's gaze could follow

Date of examination	Shot	Sibling order	Surname	Age in months and days	Sex
Date of birth	Weight at birth		Christian name	Status praesens	

Description of sound sources is to be found at p M.10

Rattle	Bell	Sand-cyl.	Stop-watch	*Cradle	P	P	Pl	Mini-music box	Whisper	Other sources	P T	Voice

Tester's questions + anamnestic information: Pregnancy — Delivery — Stat.pres. Type* A O E I

Hearing
Eye fixation Glance follows
Smile? When.
Breast feeding
Grasping Grip
Cooing When?
Articulation
Other inform.

Own disturb. Result:
External disturb.
Noise level
Becomes silent when mother speaks

) Means Attention *Orientation Eye contact Interest cf table C.4 p C.4

Fig M.9
Protocol card used at examinations of 430 Stockholm infants in the main investigation of selective attention [4].

Front side above. Reverse side below

Surname			Sex
Christian name	WBC-name: ______________	Date of birth	

Marital status Vocation

Father born

Mother born

Not.

Tester assessment

WBC's judgment

Other inform.

Methods of the examinations and reporting system [4]

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to orient with stabile head movements in the firm direction of the sound source

The visual stimulus was shown about 0.4 m in front of the baby's face. To check that the baby's gaze could follow

Date of examination Date of birth	Shot	Sibling order Weight at birth	Surname Christian name	Age in months and days Status presens	Sex

Description of sound sources is to be found at p M 10.

Rattle	Bell	Sand-cyl.	Stop-watch	Cradle	P	P	Pl	Mim-music box	Whisper	Other sources	P T	Voice

Tester' questions + anamnestic information.	Pregnancy Delivery	Stat.pres. Type* A
Hearing?		O
Eye fixation? Glance follows	———— ——	E
Smile? When?	Own disturb. Result:	I
Breast feeding?		
Grasping? Grip?		
Cooing? When?	External disturb.	
Articulation	Noise level	
Other inform.	Becomes silent when mother speaks?	

*) Means Attention *Orientation *Eye contact Interest cf table C:4, p C.4

Fig M:9
Protocol card used at examinations of 480 Stockholm infants in the main investigation of selective attention [4].

Front side above. Reverse side below

Surname Christian name	WBC nurse: ______ ______	Date of birth	Sex
	Marital status	Vocation	
Father born			
Mother born			
Nat.			
Tester's assessment			
WBC's judgment:			
Other inform.			

a stimulus the tester moved the red stick to and fro first horizontally then vertically Even at an early stage the baby will combine his visual attention with stretching his hands towards the stimulus to reach for it. The sensori-motor maturity stage decides if he also can grasp

While the initial and intermediant visual contacts were held the tester had to let a short latent period pass every time If the child had the ability to grip he might grasp the visual stimulus and put it into his mouth The grip was recorded later Not until the tester regarded the visual attention as quite surely caught, was the sound source brought up as indiscernibly as possible, about 20—30 cm behind the baby's ear first at the one side then at the other The head turning response had to be quite distinct to be noted down as positive Notations were made for each sound individually as well as for each side individually

In order to achieve and re-establish a firmly settled visual contact, when dealing with extremely attentive, lively and well developed babies, the tester had to handle the testing procedure not only quickly but decisively One cannot take for granted that the baby does not search for something he has caught sight of in the corner of his eye if the firm eye contact is allowed to slacken between the different sound presentations.

The indispensable eye contact forced the tester to keep control from the front the whole time Therefore the preferable sound sources were the small ones which could be concealed completely in the clenched fist of the tester

It is almost impossible to maintain an accurate standard distance from a baby's ear The liveliness of many infants and the difficulty of obtaining cooperation without permitting head movements, make compromises necessary As the aim was not to perform an audiometric hearing diagnosis, however but to study selective attention behavior the 20—30 cm distance should be regarded as quite an acceptable norm.

Even though the sound sources wer presented rotated, the whispering was always presented when the mother had taken the baby in her arms preparing to leave so that the baby already was looking at the door Thus for practical reasons his attention was distracted in a natural way from the tester who whispered [sss] first, then his name or pet name from an angle behind, at a distance of around 1 meter fig M 10

Fig M 10
Principal course of an examination during the mai investigation continued on opposite side [4].
It was thought necessary to take the photographs using calm and w ll developed 10 months old girl because of the additional, visually distracting stimuli consisting of the camera and the photographer



The tester gets to know mother and child while noting anamnestic information. Eye contact is established with the infant before the visual attractions are presented.

Fig M.10 continued

Photo Ingrid [illegible]



The red wooden stick, found to be sufficiently visually stimulating, attracts the attention of the infant.





The sound stimulus presented here is entirely concealed in the hand. The girl orients quickly in both directions towards the concealed sound.

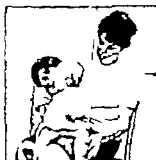


The Montessori sand-cylinders were used with a conditioning technique. The girl has been visually attracted by a red-"headed sand-cylinder. The mother has to assist the tester during this presentation in order to ensure that the girl does not look after some visual stimulus. Note that the girl holds the red-headed sand-cylinder in her hand when the mother presents the sound from the blue "headed cylinder





The *bell*" as well as the *cradle*" sounded when moved around the infant's body



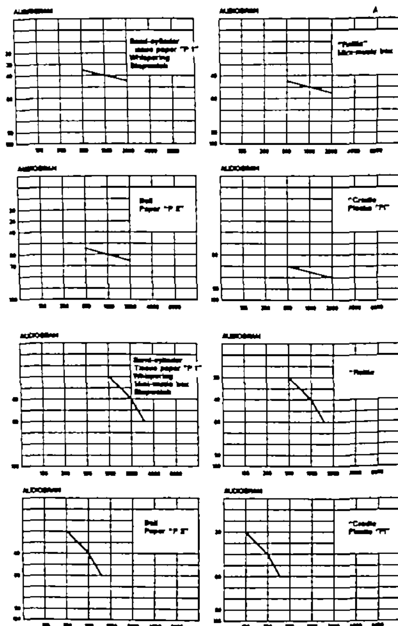


The concluding *whispering* was usually performed when the mother was on her way out. Here, the whispering test could be performed in the manner shown. The girl is still holding the sand-cylinder



At the end of the WBC reception time, the tester was able to go through the day's cases with the WBC-nurse and to check anamnestic information and assessments.

Fig. M.11
Average audiograms for pupils from the Alvik School for hard-of-hearing children compared t the relative audibility of sound sources used for studying attention behavior in infancy [5].



Perceivable to most hard-of-hearing pupils in Stockholm are,
regarding flat loss type (N=34): cradle plastic,
regarding "high-tone loss type (N= 6): cradle plastic.

Not perceivable to any hard-of hearing pupil in Stockholm are,
regarding flat loss type (N=34): sand-cylinder tissue paper whispering, stopwatch,
regarding high-tone loss type (N=.6). sand-cylinder tissue paper whispering, mini-music box, stopwatch.

Response criteria [4]

Positive response to each individual sound presentation was notated. The criterion of a *final judgment* to be positive though, was decided to request *head-turning after at least 4 of 5 presented sounds* If the infant responded to less than 4 stimulations, or if he did not at all respond to stimulation, there was a negative final judgment. This meant a deliberate restriction—to avoid the risk of too hasty conclusions The criterion, thus, was harder than the short attention span of this age, and the easiness to get distracted, on principle ought to motivate.

The need of calibration [5]

The sound sources had to be estimated regarding their possibilities to combine the following important qualities of:

a) being interesting and attractive to infants,
b) being easily and practically manageable by one tester
c) being inaudible to infants with such hearing defects which impede spontaneous speech development regardless of residual hearing.

This necessitated a calibration of complex sounds like those of the bell or the mini-music box. They were attractive to infants, handy to the tester but more difficult than pure tones to relate to sound components of importance to speech acquisition.

The following suggestion was decided upon. Audiograms of satisfactorily measured hearing defects could be taken as reference basis, giving the practical limits of audibility to hard-of-hearing infants. Schoolchildren with such audiograms, and mature enough to be able to report about their auditory perception, could offer a more reliable estimation of the audibility than a mere physical measurement like that of the sonagrams.

The sounds of the applied sources were presented to pupils of the Alvik School in Stockholm representing different types of reduced hearing. Even though their hearing defects had seriously affected their speech, they had acquired enough language to be able to tell about their reactions In the same way as for the infants, the sound sources were held at a distance of 20 cm from behind either ear Two persons cooperated, one sitting in front of the pupil, noting his answers, and checking that he could not catch sight of the sound source in the peripheral area of his visual field.

On the basis of the hearing loss type the number of pupils were divided into two main groups, A and B The procedure is described (in Swedish) in Läkartidningen by Barr and Stensland Junker[7]

Group A displayed impairments of mainly flat loss type, that is slowly decreasing hearing with increasing frequencies. The hearing impairments were ranked according to the average hearing loss at the frequencies of 500 1 000 and 2 000 Hz on the best ear

Group B displayed impairments of mainly high tone loss type, that is rapidly decreasing hearing at increasing frequencies. The hearing impairments were ranked according to the highest frequency at which the middle of three hearing values could be placed at 40 dB —which meant that the hearing on this level was better than 45 dB

The children s ability to perceive the different sound stimuli was correlated to the grade of their pure tone audiometric hearing reduction as is shown in fig M 11

The Montessori sand-cylinder the crumbling of soft paper whispering, and the stopwatch produced sounds which none of the hearing impaired schoolchil dren could perceive From practical view point these sound stimuli were hard to present invisibly to small babies. More over their sounds did not arouse the same immediate curiosity and interest as e g. the little jingle bell.

Sounds from the plastic rattle and the mini-music box were not perceived by children belonging to group A 2, B 1 and B 2. Hearing impairments of type A 1 have practically no influence on the premises for a quite normal communicative behavior and a spontaneous speech learning. This means that the sound sources which are found within the audiographic average of hearing impairments, grouped A 1—2 respectively B 1—2, from the acoustic point of view have satisfactory qualifications regarding the ability to reveal such severe hearing defects which impede the language acquisition and communicative speech development.

The little jingle bell had acoustic components perceivable to children with hear ing impairments grouped A 1—2 re spectively B 1—2, but not to the rest of the children. Thus, the most easily handled sound source did not possess all acoustic qualifications, acceptable to cover the need for an auditory stimulus revealing all hearing impairments of importance to speech development.

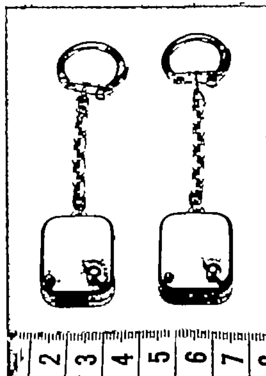


Fig M.1
The attractively sounding and easily hidden mini-music box had the disadvantage to need winding up and was audible to some pupils with hearing defects impeding spontaneous speech learning.
Photo Karolinska sjukhuset

Methods of the follow-up [6]

When speech development should be called for as finished in a child has not been settled, and the borderline between the ability of active language expression and other means of communicative be havior is fleeting.

A series of items were constructed in accordance with some general child de velopment principles. It included the much used and well-known tower-building ability[82, 83 etc.] the capacity of discriminating and naming colors of recognizing and combining forms, of under

Table M 4 *Description of items for follow-up* [6]

Free name (in Swedish within brackets)	Description	Purpose
1 Teddy ("Nalle"), fig M.13	Punch-puppet	Initial contact medium, also used for the check-up of eye-fixation and capacity to follow visual stimulus horizontally and vertically
2. "Tower" and Bridge ("Bygga-torn resp. "Bygga-port"), fig M.14a—b	Twelve wooden, dark blue cubes, ½ cm³ from Terman-Merrill (Hellström") Intelligence Test Battery	Check of ability to understand verbal *instruction and to manipulate things*
3 The Color-Boat" ("Rundturen"), fig M.15	Boat-formed play tool *(intended for sensory* training) with 6 wooden "passengers" who fit into 3 pairs of holes. Passengers" and holes are painted each two red, two yellow and two green	Check of ability to understand verbal instruction and to discriminate and name colors. Manual motor capacity and handedness, etc., are observed
4 Switch-back and Change feet" ("Rutschbanan resp. "Byta fot"), fig M 16	Platform, 47 cm from floor with staircase, three steps, and a slide, 1 m long, 35 cm wide, running to the floor	Check of big motor activity and ability to change steps on staircase-walking
5 Pig-Board" with colored balls ("Kulbrädet"), fig M 17	Rectangular wooden board, 30 × 50 cm, with holes, ½ cm diam., matching pigs on balls, colored red, yellow blue and green	Check of capacity to name colors and to make pattern after nonverbal instruction (color-identification)
6. Name pictures ("Nämna bilder"), fig M.18	Wooden boards with 12 pictures, showing a puppet, jug, dog, a stool, sand-bucket with spade, toy car a toy train, truck, flower a ball, a teddy bear	Check of speech development with regard to ability to name things on pictures adequately Observations of phonematic development level in speech, sentence building capacity and phonetic realization of utterances
7 Hiding-box ("Gömlådan"), fig M.19	Basket with cover containing toys related to the pictures of wooden boards above, 6.	Check of capacity to match objects and pictures of the same category see 6.
8 Form-box ("Form-plock lådan"), fig M.20	Wooden box with holes formed to match different forms: round, square, triangular rectangular and twelve-sided-form	Check of spatial ability capacity to combinate, handedness and fine motor development
9 Star" and Table ("Stjärna resp. "Bordet"), fig M.21	Wooden star, golden color little toy table	Check of phonetic realization regarding pronounciation of the Swedish phonemes /ʃ/ /ɳ/ /ɖ/
10. Pure tone generator manual, P T" figs M.4 M 22—23	Pure tone generator 3,000 Hz with 5 intensity levels, see also fig M 8 (sonagram)	Free field hearing test; sound presented from pure tone generator hidden in puppet shelter
11 Hand-bell" ("Ringklockan") fig M.24	Small hand-bell, brass, with wooden handle, see also fig M.8 (sonagram)	Informal hearing test for checking f sound attention

standing pictures, of classifying objects, of motor development, stepping on a stair case, [8-29] etc

Eye fixation and the ability to follow a visual stimulus horizontally as well as vertically were examined. An informal free-field test to check up the organic hearing was made Purely linguistic tests were given for phoniatric and phonetical reasons

The follow-up took place at the "Lekotek" an agency for child and parent guidance in which training through systematic play activity with the help of educational toys is practised[159]

Some of the well-baby clinic localities had been changed during the two years. This meant that some of the children would have been familiar with the environment, and some strange to it. Therefore, it seemed preferable to choose a milieu which was new to all children At the same time it presented a more detached, quiet and attractive environment. Table M 4 describes stimuli used

It was regarded as suitable to summon children who in the first place, at least two years after the infant investigation would be distributed around the level of 3 years

Thus, summons were sent to the parents of these children, reminding them of the infant investigation made two years earlier and informing them about the follow-up For practical reasons it was found to be desirable not to extend the study to more than three weeks In order not to risk losing the voluntary cooperation of the parents, it was decided that the follow-up should not coincide with the summer vacation

It should be emphasized that the time span of 2 years has to be an approximate one, since the main investigation was going on during half a year and the follow-up was made during 3 weeks

When the summonings were planned the investigator was fully aware of the risk that many infants could have disappeared" from the card-index, either because of diminishing interest and/or need with regard to health-control.

A schedule was made in order to avoid waiting hours and the parents were told alternatives as far as possible The protocol cards were following the same principles as the cards used in the infant investigation, fig M.25 Examination date and birth date were thus combined in the same way so that the actual age easily could be computed. Anamnestic data included the mother's opinion of the child's developmental status.

A necessary claim was that the follow-up study of a child was made without the tester knowing about the result of the infant examination in advance to avoid the risks of a biased report. The research assistant who took care of the summonings was not allowed to know about the results of the infant examinations. The card index was not kept available during the follow-up study Not until the end of the follow up examination were the results from both studies compared

The follow-up examinations were undertaken by the tester/investigator and a speech-pathologist. They alternated so that one of them tested and the other reported The preschool teacher employed at the "Lekotek participated in 12 of the examinations.

The status of speech development was reported in accordance with a schedule worked out by the speech-pathologist. It is shown summarized in table A.2, Appendix I. The speech description includes phonematic, grammatical and semantic notes. Quantitative measurements regarding vocabulary were not considered possible because of lacking reference basis.

Procedure of examinations and response criteria [6]

While anamnestic dates were noted the child was diverted from the conversation by some distracting and attractive toy The mother and/or father were asked the necessary questions in a soft, low voiced way by the reporter Stress was laid on trying to get the child to act and speak as unconstrainedly as possible.

The presentation procedure is described below The criteria were settled with the guidance of foreign tests and Hellström's Swedish translation of Terman-Merrill. The description follows the same order as is used in the tableau above table M.4 p M.23

1 Teddy (Nalle) was used initially as a means of greeting, fig M.13 Thereafter the eye contact was checked up as well as the child's ability to follow to both sides and up-and-down with his gaze In order to be regarded as a positive response a firm eye contact was demanded for all ages as well as an initial visual interest, e.g. manifested in trying to greet, talk, laugh, trying to avoid Teddy or hide from him, pat him etc., moreover when the child's eyes followed Teddy horizontally and vertically Negative response meant a complete indifference

2. Tower and Bridge (Byggatorn and Byggn-port) meant that the twelve cubes were laid in front of the child who was asked. Can you build a tower out of these? figs M.14a—b If the child started to build by himself, he was allowed to do so until he got tired of it. If he did not show an interest in the cubes, or if he did not make the impression of having understood the meaning of the words, the tester started to build a tower out of the child's reach, then moved the cubes within his reach, saying:

Try to build the same tower yourself.

If the child had succeeded in building a tower the tester took three cubes and built beyond the reach of the child a Bridge by placing two cubes beside each other with a space in between, big enough to form a kind of passage. Then the third cube was placed upon the two other cubes.



Fig M.13
Check of eye contact started the follow-up
Photo Ingrid Nordström

standing pictures, of classifying objects, of motor development, stepping on a stair case, [8-23] etc

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Then the tester asked. Now this red boy/girl is going on board again to get home for dinner He/she takes his/her place. This is his/her place " The tester showed how the red figure was put down into the red hole. Can you show me where the other boys/girls should sit?

The Color Boat did not call for the ability of naming the color nor for the strict execution of the request to take the red boy/girl, when the child was <2 years 6 months. On the other hand it was requested, for all ages, that the child himself be able to put the different wooden figures in their appropriate holes after having been told and shown one figure by the tester For ages <2 years 6 months the moving of the figures and putting them into the holes was allowed to take 60 seconds, for older children not more than 40 seconds.

4 The Switch-back (Rutschbahn) had not only the purpose of giving an opportunity to check the big movements and the ability to change foot in the staircase cf fig M.16 It was also meant to motivate the child to cooperate and make him less tense and shy If the child showed that he liked sliding he was allowed to do it for a while.

The Switch-back called for the changing of feet for all ages >2 years 9 months. Notations regarding motorics and/or the attitude to the items was not judged as positive/negative More trials were allowed, as it was regarded as normal and natural to show cautiousness at the confrontation of the switch-back. If the changing of feet, however did not occur at all or if the sliding was left out, the notation was negative

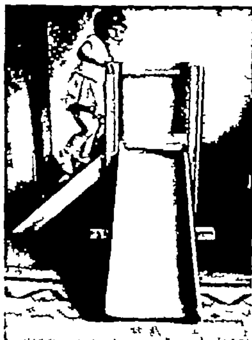


Fig M 16
Photo Stan Dietrik Bellander



Fig M.17
Photo Stan Dietrik Bellander



Fig M 18
Photo Sten Didrik Bellander

5 The Pig-Board ("Kulbrädet) with balls presented a more advanced test regarding the ability to identify colors, understand their names and name them, fig M 17 The tester put a little row of balls in the holes mostly two red ones, one yellow one and one red again. The tester taking a red ball, asked. "Can you tell me what color this ball is?" If the answer was the wrong one, or the child did not answer at all, the tester said "Take a red ball." If the child was not able to take the right ball, the tester took a red ball and gave it to the child. "There you are It is a red ball. Can you put it in the hole beneath this other red ball?

If the child succeeded, the tester asked him to put the balls in the same way as the tester had done "Can you make the same line of balls as I have made? Then the tester continued with the other colors and tried at first to find out if the child could name the color of e g. the blue ball. If he did not name the ball s color the tester examined if the child could take the same color make the same line, etc

The Pig Board was used as a check up of earlier manifested ability to discriminate colors and a guiding information regarding motorics A complete incapacity to follow the tester s pattern was noted as a negative" response.

6 Name pictures" (Nämna bilder) was a verbal test which demanded that the child be able to tell what the twelve pictures meant, fig M.18 Because of the age level of the children, names and interpretation of the pictures were accepted within reasonably wide frames. (It has been regarded as meaningless to present the children s alternatives here since they are reported in Swedish.) The pictures were *the following:*

Girl with yellow hair red dress and white apron, yellow mug with red fluid in it, black-and-white dog, red stool red bucket with sand and yellow spade, red toy car red toy train, red truck with yellow platform and cargo white daisy



Fig M 19
Photo Sten Didrik Bellander

four-colored ball, toy duck floating" on the water brown teddy-bear

Name pictures requested the identification of at least 4 pictures out of 12 for all ages <2 years 6 months Compulsory *identification was requested* regarding the girl, the flower the ball and the teddy-bear cf fig M.18 For the ages >2 years 6 months to <2 years 9 months at least 6 pictures had to be identified and for the ages >2 years 9 months at least 10 pictures had to be requested as to identification. Acceptable alternatives are referred to (in Swedish) *in the Appendix II The phonetic* realization of supradentals was not influencing the judgment of positive/negative response

7 The Hiding-box (*Gömlådan*) completed "Name pictures by revealing the child's capacity to understand categories fig M.19 The tester started by taking a red ball out of the basket, saying: I have hidden a few things in this basket. You will help me by showing me to which pictures those things belong This (ball) shall be put on the picture



Fig M.20
Photo Sam Didrik Bellander

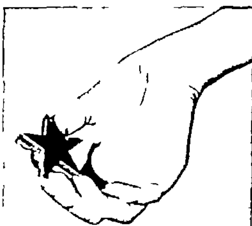


Fig M.21
The speech follow-up was closed by check up of supradentals.
Photo Karolinska sjukhuset

which you think resembles it most of them all.

Then the following things were taken one by one, out of the basket: a little puppet, a toy car a plastic bird, a plastic cup and spoon, a grey dog, a plastic lily *of the valley a toy train* and *a jeep* a teddy-bear and a toy chair The child was successively told to categorize the objects by putting them on the resembling pictures

The Hiding-box did not require quite correct correlations and/or adequate answers for ages <3 years and [illegible] that the only pictures which called for categorizing were the mug with the [illegible] fluid, the black-and-white dog, the [illegible] and the teddy-bear

8 The Form-box (*Form-[illegible]* dan) was intended to test the [illegible] spatial ability The tester showed [illegible] the cylinder and kept the [illegible] form hidden behind her back At first [illegible] the round form was presented [illegible]

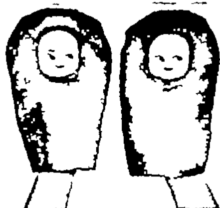


Fig M.22
An informal hearing test ended the follow-up of this and the opposite page
Photo Karolinska sjukhuset



Fig M 23
Photo Sten Didrik Bellander

which the square one followed then the rectangular the triangular and finally the twelve sided form, cf fig M 20

The "Form-box" demanded for the ages >2 years 6 months at the least, the capacity to find the adequately formed holes for the form round/cylindrical and square/cubical. For the lower ages unsuccessful trials were allowed

9 The Star" and the toy Table" (Stjärnan" respectively Bordet) completed the verbal tests, fig M.21 The tester kept the star in its handle and asked "Can you see what this is?" Then there was noted, both if the child could find the adequate name and how he realized the Swedish ɛ:/ and the supradental sounds /ʃ/ ɳ as well as ɖ/ in the Swedish equivalent to table [bu.ɖ]. If the child seemed tired or uninterested, the tester tried to show at a table in the room next to the examination room etc. in order to get a possibility to note his realization of ordinary supradentals in Swedish

The Star and the "Table were two items which did not at all request response in the form of adequate phonetic realizations. The pronounciations were noted but did not cause judgments of positive/negative character The phonetic description was regarded as a valuable information concerning speech development and nothing more

10 The pure tone test "P T was first presented with the generator hidden within one of two different punch-puppets a dog and a cat. This was an explorative trial, in order to investigate if children at this age level respond to a visible difference rather than choose between two identical, visual impressions when listening to a sound in order to point to its origin.

After this trial the tester hid the pure tone generator kept in one hand by putting on felt covers with smiling faces on both hands, figs M 22—23 The child was told to listen if he could hear one of the puppets say something, and if he could point at it. The response was combined with that of the "Hand-bell but mainly regarded as methodological experiment.

11 The "Hand-bell (Ringklockan) fig 24 requested a distinct turning of the head when the sound was presented at a distance of 1 meter diagonally from behind. Only one head-turning in each direction was needed. The fast extinction of attention and interest at the three years of age level was expected.

The informal bell-test was completed by the pure tone test for quite a special reason. Many parents had namely expected some sort of a formal hearing test of the pure tone type They connected the follow-up with older children's hearing tests at the 4 years of age level which had become actual just then.



Fig M 4
Photo Karolinska sjukhuset

Fig M.25
Protocol card used at the follow-up study of consecutive communicative behavior and speech development in 87 Stockholm children [6]

Front side

Date of examination Date of birth	Pure tone / Sibling order Weight at birth		Surname Christian name	Age in mths and days Status pres.
Eye contact?	Follows "Teddy"?	Knows about "color-boat"?	Names pictures?	Type of reaction:
Tester's questions and anamnestic information:		Pregnancy Delivery		Own disturb.
Hearing				
Smile:	Adequately	In the "wrong" way	Serious	Result:
Grasping	Fine Right-handed	Adequately Clumsy Left-handed	Inadequately	
Speech				Listens?
At what time				Answering
Sentences				Words

Fig M.25 continued *Reverse side*

Surname			Sex
	WBC nurse ____________	Date of birth	
Christian name			
		Marital status	Vocation
Father born			
Mother born			
Nat.			
Tester s assessment			
Switch-back	Change feet	Motor behavior	
Tower -building No.?		Pig-board"	
Bridge	Form-box	Color recognition	
	Hiding-box	naming	
Speech development (phonetic realizations at separate card)		Star pronounc.	("Stjärna")
		Table	("Bord" resp. "bordet")
Other inform.			

Methods for examinations of children 4 years of age [7]

The so-called 4-years-of age check-up p I 4 is intended to be performed in Sweden as a routine comprising a general health control of all children. Physical health hearing, sight, speech development and mental functioning is to be checked. The larger share of the control is expected to be handled by the WBC-nurse e g. ordinary physical examinations weight, length, blood tests, micro sedimentation, etc

Eye mobility in different directions is checked by the WBC nurse who is per forming the so-called Nyman s Cover test, checking assymetric eyes and strabis mus Eventual shortsightedness or other visual deviations are checked by Snellen s E shown and described in fig M.26

Moreover the nurse is intended to interview the mother or the father or the one who has the main responsibility for the care of the child, regarding mental social, and emotional conditions The WBC nurse consults the pediatrician and if they feel inclined to call for the psychologist, if there is any they may suggest a specialist examination which takes place if the parents agree

The pediatrician or the doctor on duty at the well-baby clinic, is supposed to make a general examination regarding physical health, motor development, general behavior and mental functioning such as observed at different given situations, e g. balancing, drawing, cutting with scissors etc.

Speech development and hearing examinations are in Stockholm delegated to



Fig M.26
Snellen's E used at WBC examinations and 4-years-of-age check-ups [7].

As the child cannot read at 4 years of age, he has to show in which direction the "Snellen E" that the WBC-nurse points out to him is placed, by turning an E with a handle in the same direction. The child sits on the lap of the mother at a distance of 5 m from a table with Es turned to either of both sides, upwards and downwards. One eye is covered.

a special clinic, furnished with a sound-proof chamber. Hearing is examined by Barr's[3] method for play audiometry performed with the aid of an audiometrist. Speech development is examined by interviewing the mother or the one who has the main responsibility for the care of the child. Thus, the mother expresses her opinion as to the child's level of articulation, semantics, etc., in a ranked comparison with the level of most other children.

Follow-up with help of "4-years-of-age check-up" [7]

The health control program, however has not been carried through in Stockholm to the expected degree as yet. Medical staff in the necessary categories has been lacking. The hope of utilizing the results of the 4-years-of-age check-up optimally thus came to nothing. The minor follow-up which could be accomplished is not complete.

Within the practical-economical frame work of the investigation, the only possibility was to utilize the available WBC notations from the "4-years-of-age check up" for a comparison with the results of the infant examinations. Many of the infants had moved from the district or finished their regular WBC examinations at the time of their being 4 years old.

STUDY MATERIAL

Geographical location and study objects for infant examinations [2] [3] [4]

For practical-economical reasons the investigation was limited to the Stockholm area. It seemed favorable to utilize the comparative accessibility of infants under one year of age at city well-baby clinics. For the preparatory methodological work, though it appeared desirable to look for more secluded conditions. A suburban infant nursery home suited this purpose.

The aim of the *minor study* does not motivate a closer presentation of socio-economic conditions It could be observed, though, that infants stay in Swedish nursery homes mainly for the following reasons social handicaps, planned adoption temporary illnesses or other complications for the mother and/or family members, sometimes also physical and/or mental handicaps in the baby himself Mostly the stay is intended to be a short term one and the nursery homes are on principle not meant to keep infants after the age of one year The minor study at Klingsta spädbarnshem Danderyd comprised *26 babies ranging from > 1,0 to < 10 months 13 boys and 13 girls* [2]

The *pilot study* performed afterwards was located to the same Stockholm well-baby clinics as the main investigation. Its purpose, to form a methodological preparation for the main investigation, makes the presentation of socio-economic conditions sufficient, which concerns the main investigation below The pilot study comprised *134 infants aged between 2—14 months 68 boys and 66 girls* [3]

The considerable range of ages in the *main investigation* was, finally regarded as favorable because of the possibility to obtain a clear impression of upper/lower age limits for an examination of manifest selective attention. The main investigation comprised *480 Stockholm infants ranging from ≥ 2½ months to ≤ 13 months of age 265 boys and 215 girls* [4]

Comment on the choice of WBC registered infants [3] [4]

Representativity Well-baby clinics were regarded as reflecting a reasonable cross-section of the Swedish society since 97% of all infants under one year of age were registered in 1965 when this study was designed[153] and slightly more in 1966

Table S 1

Age and sex distribution percentage and a *o' 480 Stockholm infants examined in the main investigation* *r* [4]

Ages in months and days	≤ 3.0 months	3.0 — 3.29	4.0 — 4.29	5.0 — 5.29	6.0 — 6.29	—			) — 2)	11.0 — 11.29	12.0 months and older	Total
% ♂ 55.21	5.6	9.4	9.9	11.3	15.5				9	8.0	5.7	Σ 100.0% boys
% ♀ 44.79	6.0	11.1	7.4	10.2	10.0			ı	11.6	7.0	6.5	Σ 100.0% girls
Σ 100.0 %	6.0	10.1	8.8	10.8	12.9	1	1	1(	10	7.5	6.0	100.0 % All
Absolute frequency	28	49	42	5	6..	3	4	51	49	36	29	480 All
Boys	15	25	6	30	41	0	3	.5	4	21	15	265 boys
Girls	13	24	16	2	1	1)	20	6	25	15	14	215 girls

when it was started, cf Stensland Junker[188]

In the city of Stockholm 94.5% of all living births were an average figure for registration during the first year of life, as reported by the Child Welfare Board of Stockholm regarding 1965 when most of the infants examined were born.

It is possible that the frequency of appointments was relatively higher in the country than in Stockholm due to the fact that a large city appears to provide more opportunities to choose e.g. private doctors for the health control of babies. Throughout the country the visits to well-baby clinics were most frequent for babies during their first year of life. (Later on, the frequency always decreases year by year until school age is reached, cf Stensland Junker[188] p 49)

Sex ratio The study comprises 44.8% female and 55.2% male infants. On 1 11 1965 there were 4 847 boys and 4,625 girls under 1 year of age in Stockholm[182] I.e. 48.9% female and 51 1% male infants The difference was disregarded As far as was known there had not been any systematic study accomplished regarding differences in sexes as to selective attention in infancy Anecdotal observations reported that boys learn to speak later than girls but the slight disproportion was considered as marginal. The percentage method of comparisons was considered to cover the risk for over interpretation.

Milieu factors The longitudinal investigation—a part of a comparing international program—presented by Karlberg et al.[89] and Klackenberg[101] shows the influence of environment on child development. Thus, children from the highest social class are reported to develop more slowly than those from the middle and lowest classes during the first six months of life Between 9—12 months there is no significant difference, but during subsequent years there is a faster development for children from higher social groups (p 90)

The distribution of parental ages refers to the time when the infants were examined. In the total sample, there were 5 mothers and 1 father 16 years of age. The oldest mother was 43 years, and the mean age of the mothers was 24 years. The ages of the fathers range between 56 years and 16 years with the mean age of 27 years. Fig S.2 shows how the ages of the mothers compare with the general distribution regarding ages of mothers in Sweden 1965[183]

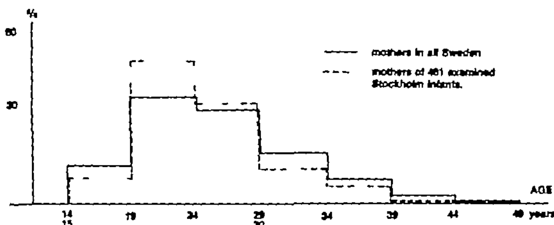


Fig S.2
Ages of mothers in Sweden 1965 compared with the ages of 461 mothers in the main investigation of selective attention infants (4).

It should be mentioned that the more spread-out distribution of Swedish mothers in general is caused by factors, which do not lie within the scope of this study e g conditions in rural areas.

Possible changes in the socio-economic distribution during the decade between the beginning of the Karlberg et al. investigation[9] and this present one will not be commented either The tables above are shown only in order to give an approximate description of a population of infants registered at well-baby clinics of the inner city area. The study material may be said to satisfy reasonable requests of the aims The ratio between the sexes though, does not conform entirely with the corresponding ratio in Stockholm as a whole

WBC staff The majority of the infants were recruited from the well-baby clinics reported below Three of the clinics had the same doctor throughout the study The two others each had different pediatricians, one of them being replaced by a locum during the study period Four of the WBCs had permanent nurses, and one had 3 different nurses during the main investigation

Environmental variations, influenced by changing staff was regarded as having no importance The tester was unchanged throughout, and the tester's protocols provided the basis for the analytic and statistical treatment of the material.

Table S 4

Stockholm inner city WBC-districts represented in the main investigation [4].

The main investigation comprised 480 infants,
registered at Stockholm WBC were 448 "
from Klingsta and other WBC " 32 "

Well-baby clinic for district	Absolute number of examined infants		Percentage of new registrations in 1965 within the district %	of absolute N registrations
Norrtull		131	66.8	196
Johannes-Ekhagen	89			
Johannes-Hjorthagen	58	147	56.7	259
Norra Vasastaden		98	56.0	175
Södra Vasastaden		72	42.0	172
Total		N = 448	55.8	802

The lowest percentage of infants against the background of new registrations concerns the WBC having changed staff during the investigation.

The high percentage of first births in table S.5 is conditioned by the environment being that of an inner city. The eventual effect of sibling order on selective attention behavior had not been investigated so far.

The logical explanation of the fact that city center children to a larger extent are first births is that the communities, as a rule do not provide enough accomodations, necessary for family size increases. Thus, a relatively greater number of families with several children reside outside the cities, more or less forced to accept accomodations in the suburbs.

Table S.5

Percentage distribution of first and latter births as reported by 469 mothers of Stockholm infants examined in the main investigation of selective attention [4]

Pregnancy order for the mothers of the infants	1 st pregnancy	2nd pregnancy	3rd or >3rd pregnancy	twins irrespective of order	stillborn previous children	1 previous miscarriage	or > 2 previous miscarr
N 469 = 100%	65.8[illegible]	24.57	6.41	0.43	0.64	1.28	0.85

The distribution of parental ages refers to the time when the infants were examined. In the total sample there were 5 mothers and 1 father 16 years of age. The oldest mother was 43 years and the mean age of the mothers was 24 years. The ages of the fathers range between 56 years and 16 years with the mean age of 27 years. Fig S 2 shows how the ages of the mothers compare with the general distribution regarding ages of mothers in Sweden 1965[133]

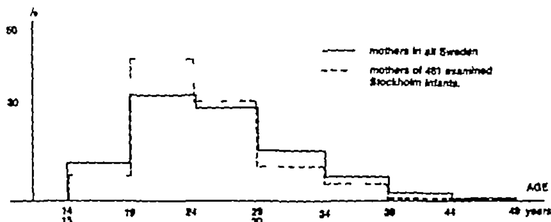


Fig S 2
Ages of mothers in Sweden 1965 compared with the ages of 461 mothers in the main investigation of selective attention infants [4].

It should be mentioned that the more spread-out distribution of Swedish mothers in general is caused by factors, which do not lie within the scope of this study e.g. conditions in rural areas

Possible changes in the socio-economic distribution during the decade between the beginning of the Karlberg et al. investigation[93] and this present one will not be commented either. The tables above are shown only in order to give an approximate description of a population of infants registered at well-baby clinics of the inner city area. The study material may be said to satisfy reasonable requests of the aims. The ratio between the sexes, though, does not conform entirely with the corresponding ratio in Stockholm as a whole.

WBC staff The majority of the infants were recruited from the well-baby clinics reported below. Three of the clinics had the same doctor throughout the study. The two others each had different pediatricians one of them being replaced by a locum during the study period. Four of the WBCs had permanent nurses and one had 3 different nurses during the main investigation.

Environmental variations influenced by changing staff was regarded as having no importance. The tester was unchanged throughout and the tester's protocols provided the basis for the analytic and statistical treatment of the material.

Study material for follow-up by reports from the 4-years-of-age check-up [7]

Although the trial to obtain a second follow-up met with difficulties, there were found to be 32 children still registered at the WBCs of the main investigation, who had been submitted to "4-years-of-age check-up Another 19 could be traced to other agencies, so that this follow-up finally could be performed for *51 children, ranging from 4—5½ years 25 boys and 26 girls*

Study material for the trial application of results—BOEL [8]

The newly constructed sound sources of the BOEL selective attention screening test were submitted to clinical calibration at the Alvik School for hard-of-hearing pupils In all, 112 pupils had helped with the calibration, some participating in the main investigation only some over lapping i.e. participating in both calibrations. The BOEL calibration comprised *72 hard-of-hearing pupils ranging from 7—17 years 40 boys and 32 girls*

During the preparatory work for BOEL the new ideas of a simplified set up were tried at WBCs in Bagarmossen, Farsta Hammarby and Tensta. The trials were undertaken by a WBC-nurse and the tester alternatively and comprised *26 infants ranging between 5 months 2 days and 10 months 18 days 13 boys and 13 girls*

Since January 1971 the BOEL attention screening test has been made available to *85 well-baby clinics* in the Stock bolm area as a voluntary screening program for *infants ranging from 7—9 months*

RESULTS

The main investigation [4]

The results answer the questions a)—d) at pp I.2 Since the two explorative studies [2], [3] have been accounted for in Methods tables M 1 M.2, and fig M.3 they will not be commented here

The percentage of positive responses in each age group is shown in figs R.1—7 for boys, girls, and both sexes The curves concern the sounds of rattle" bell Montessori sand-cylinder stopwatch, cradle" crushed tissue paper cello-cotton paper plastic, and mini-music box.

In the age interval of 7 0—7.29 months and days a kind of plateau formation is observed, more remarkable for girls than for boys. The curves for the bell and the cradle" show plateaus earlier between 6 0—6.29 months and days For the stopwatch the plateau" begins at 7 0—7 29 and for the mini-music box a first plateau begins at 5 0—5.29 and a second one at 8 0—8.29 months and days The general trend of the curves is that of an ordinary development curve.

The graphs of the Montessori sand-cylinder and the crushing of paper and plastic have a decreasing course at the intervals for higher ages thus showing more irregularities than the other curves.

There is a difference of about 2 months regarding the lowest age level for any response at all The "cradle" has given rise to responses at the earliest. The rattle" and the bell have both caused responses 1½ months earlier than the stopwatch Neither the stopwatch nor the Montessori sand-cylinder have given rise to any positive responses before the level of 4 0—4.29 months and days

The response percentage is remarkably higher for girls than for boys all along the line in all graphs, but for the stopwatch in the interval 8 0—8.29 and for the mini-music box between 5 0—7.29 months and days. It should be observed that the latter sound stimulus has been presented considerably fewer times.

The comparison between the sexes shows, furthermore, that positive responses start on the average 1 month earlier for girls than for boys, except for the stopwatch and the mini-music box

The survey of table R.1 comprises all used sound sources. It shows how many presentations of each individual sound have been done in percentage of all 480 examinations, regardless of the responses

being positive or negative. Since the sounds have been rotated as to serial order it could be gathered from the per centage to what extent it has been possib.e to present different sound stimuli.

Moreover the survey informs about the total percentage of positive responses and the type of response, viz head-turning in one direction, in both directions respec tively the searching described at p M.5 The sex differences appear as a total for all ages and have to be combined with the age distribution of the graphs, if full information is desired.

The mini-music box has given rise to the highest percentage of positive responses and the Montessori sand-cylinder to the lowest one The applicability in practice of the sound sources cannot be concluded from the mere numerical comparison of the graphs respectively table R.1 This question will be discussed further pp C:5

A completion of table R.1 is given in table R.2 summarizing the final results, according to the criterion of 4 head-turnings after 5 sounds as described at p M 21

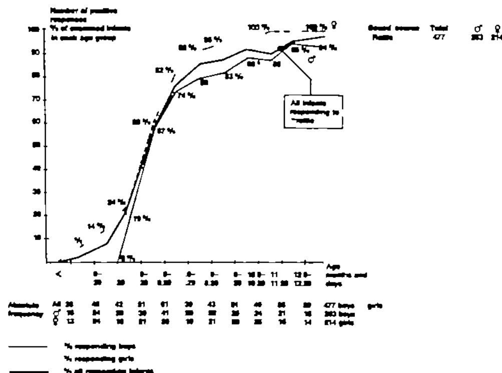
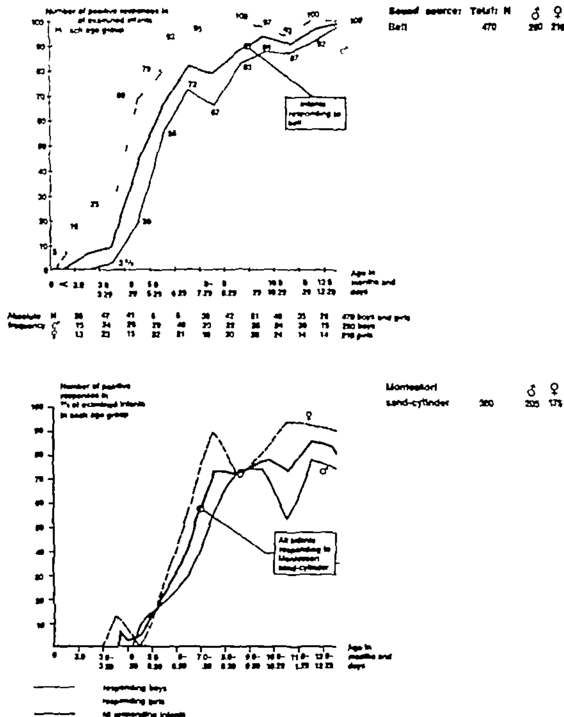
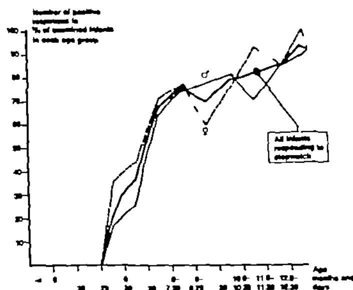
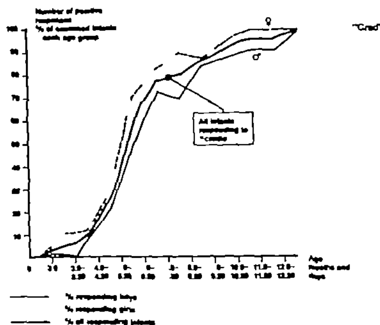


Fig R.1
Percentage of positiv responses by means of distinct head-turnings in direction f sound stimulation after initial firmly established visual attraction with regard to different sexes and age levels
(Description of the sound in table M.3 presentation course, fig M 10, sonagram fig M.8.)

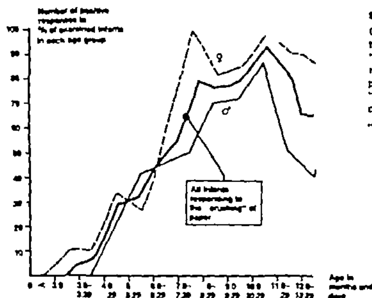


Figs R... and R.3
Percentag f positive responses by means of distinct head-t rni gs in direction of sound stimulation fter nitial firmly established visual attraction with regard to different sexes and age levels. (Description of the sounds in table M 3 presentation course fig M 10 sonagrams, fig M 8.)

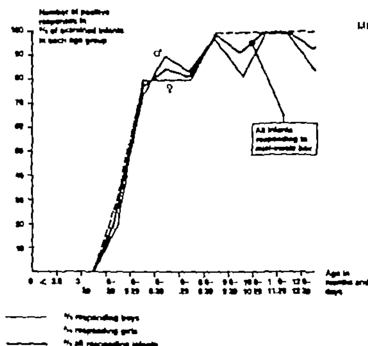




Figs R:4 and R.5
Percentage of positive responses by means of distinct head-turnings in direction of sound stimulation after initial firmly established visual attraction with regard to different sexes and age levels. (Description of the sounds in table M.3 presentation course, fig M.10 sonagrams, fig M.8.)



Sound source:	Total: N	♂	♀
Crushed			
tissue paper	304	156	148
"cellocotton	53	32	21
respectively			
plastic			
"P or "P₂			
or "P1"	118	70	48
"Crushing" totally:	475	258	217



		♂	♀
Mini-music box	148	[illegible]	[illegible]

% responding boys
% responding girls
% all responding infants

Figs R.6 and R.7
Percentage of positive responses by means of distinct head-turnings in direction of sound stimulation after initial firmly established visual attraction with regard to different sexes and age levels. (Description of the sounds in table M 3, presentation course fig M 10, sonagrams, fig M:8.)

Table R.1

Results of the main investigation regarding selective attention responses of 480 infants on sound stimulation comprising a) attention arousing quality of different sound sources b) sex differences in response ratio [4]

Sound source	Number of presentations in 480 examinations, abs. frequencies	Percentage of sound presentations in 480 examinations	Positi responses						
			abs. frequencies	Perc tage					
				Total		Boys		Gi ls	
			Total	Response type		Response type		Response type	
Rattle	477	99%	308						
Head-turning:									
1 direction				5 7		6 8		4..	
2 directions				58.9		52.9		66 4	
searching				0.0	64.6	0 0	59 7	0.0	70.6
Bell	470	98%	31						
Head-turning:									
1 direction				3..		3.8		2.4	
2 directions				28 1		25.0		31.5	
searching				35.2	66.5	33 1	61.9	38.1	72.0
Montessori sand-cylinder	380	79%	208						
Head-turning, fter mother's participation:									
1 direction				7.9		8 8		6.9	
2 directions				37.9		32.7		44.0	
Conditioning"				8.9	54 7	7.8	49 3	10.3	61..
Stopwatch	347	72%	231						
Head-turning, when mother is holding the watch.									
1 direction				10.4		1 4		8 1	
2 directions				45 0		43.5		46.6	
Conditioning				11.2	66.6	8.1	64 0	14.9	69 6
Cradle	361	76%	223						
Head-turning:									
1 direction				3.9		3.6		4 2	
2 directions				57.3		51.3		64.3	
"searching				1.2	62.4	1.0	55.9	1.3	69 8
Tissue paper and rough cellocotton respectively plastic	304 } 53 } 118 }	99%	268						
Head-turning, after instruction to mother									
1 direction				7.9		8 4		7 4	
2 directions				51.6	59.5	44.0	5..4	60 0	67 4

Table R 1 continued

Sound source	Number of presentations in 480 examinations, abs. frequencies	Percentage of sound presentations in 480 examinations	Positive responses						
			abs. frequencies	Percentage					
				Total		Boys		Girls	
			Total	Response type		Response type		Response type	
Mini-music box	146	(73%) 30%	1 1						
Head-turning, after conditioning									
1 direction				6[illegible]		4.5		8.6	
directions				70.0		71 7		67.3	
distance searching**				6.8	83.0	3 4	79.6	12.1	88.0
Whisper from behind at departing	310	64%	[illegible]23						
Head-turning:									
1 direction				[illegible]2		3.6		0 7	
directions				54 9		51[illegible]		59 4	
voiced name				14 4	71.5	1[illegible]5	67.3	16 7	76.8
Pure tone generator	125	—	—	—	—	—	—	—	—
Other sources	387	81%	230						
Reflex response:									
General "startle				[illegible]1		1.5		[illegible]8	
Blink reflex, etc.				59 4		54.9		64.6	
Discomfort, e g. crying				1.3	6[illegible]8	1.0	57 4	1 7	69 1

) The sound source was not fully usable until towards the end of the main investigation. It was relevantly presented only to 200 infants. Thus, the 73% do not regard the 480 infants of the column heading, but the 30% below By distance searching is meant that the box, when wandering around the infant's body was kept at the distance of around 1 meter

) The sound source could not be hidden from the sight of the infant, and did not interest him.

) Other sources comprise sounds from a plastic tube filled with lead pellets, two wooden rattles, a china can filled with lead shots, finger-clicking and handclapping. p M.10.

Attempt at an estimation of a lower age limit [4]

As the test series applied in the main investigation had given no positive results before 2½ months of age for girls and 4 months of age for boys, an attempt was made to scrutinize the possibilities of finding the age reasons for negative results A random sample of 60 infants having given negative results at a first testing, ranging between the age of 2.16 and 10.06 months and days at the first test, were subjected to renewed testing

The time between the first and the second test varied because of the diffi culty to get the infants to appear at the WBC at an appointed time. As is shown in table R.3 the renewed test gave in no case a positive result under the age of

Table R.2
Final results of 480 examinations in the main investigation [4]

Age in months and days	Number of examined infants			Number of negative results			Percentage of positive results		
	♂	♀	All	♂	♀	All	% of ♂	% of ♀	% of all
< 3.0	15	13	28	15	13	28	0	0	0
3.0 — 3.29	25	24	49	25	23	48	0	4	2
4.0 — 4.29	26	16	42	25	11	36	4	15	11
5.0 — 5.29	30	22	52	25	14	39	17	36	26
6.0 — 6.29	41	21	62	19	7	26	53	67	59
7.0 — 7.29	20	19	39	6	3	9	70	84	78
8.0 — 8.29	23	20	43	5	3	8	78	85	81
9.0 — 9.29	25	26	51	5	2	7	80	92	86
10.0 — 10.29	4	25	49	4	2	6	83	9	88
11.0 — 11.29	21	15	36	2	1	3	90	93	92
> 12.0	15	14	29	1	1	2	93	92	93
All ages	265	215	480	132	80	212	50.1%	62.7%	55.8%

5 months and 12 days. This result was considered in the discussion of age limits.

Nothing suggested that a repetition of the test would be *affected* by *learning* processes. The infants examined for a second time after an interval of 4 weeks or more acted in the same way as infants presented for the first time to the sound sources, which is in accordance with the findings of other investigators[19, 89]

The prediction value of the methods applied [4][6][7]

Follow-up after 2 years [4][6] Functions and abilities, as presented in table R.4 *are correlated in table R.5 with* final results of the main investigation, as presented in table R.2. Furthermore, the follow-up of eye contact, glance follows understand instruction and name pictures are correlated to eye contact and glance follows in infancy A detailed report of the follow-up examinations is found in Appendix I completing the concise table R.4

Understand instructions both regarding Color Boat and Tower show a strong positive association with *the positive final results of the main investigation* at the significance level of 0 01 thus for Color Boat $\chi^2 = 69\ 48$ and $\Phi = 89$ respectively for Tower $\chi^2 = 56\ 93$ and $\Phi = 81$

All correlations of table R.5 show positive associations, but for the item Glance follows Teddy" Furthermore Understand instructions, Color Boat Name pictures Adequate smile and Speech developed have been associated with Eye fixation and eye contact *with the tester at the main investigation*. Positive associations on the 0.01 significance level are shown, except for Glance follows Teddy" showing a somewhat weaker positive association on the 0 05 significance level. Finally Glance follows visual stimulus in infancy correlates positively with 4 of the follow up items. The Final judgment *of communicative behavior in childhood*

Table R 1 continued

Sound source	Number of presentations in 440 examinations, abs. frequencies	Percentage of sound presentations in 440 examinations	Positive responses: abs. frequencies	Percentage: Total		Percentage: Boys		Percentage: Girls	
			Total	Response type		Response type		Response type	
Mini-music box	146	(73%) 30%	121						
Head-turning, after conditioning									
1 direction				6.2		4.5		8 6	
directions				70 0		71 7		67.3	
distance "searching"*				6.8	83.0	3 4	79.6	12.1	88.0
Whisper from behind at departing	310	64%	[illegible]3						
Head-turning:									
1 direction				2.[illegible]		3 6		0.7	
directions				54.9		51.[illegible]		59 4	
voiced name				14 4	71.5	1[illegible]5	67.3	16 7	76.8
Pure tone generator	1[illegible]5	—	—	—	—	—	—	—	—
Other sources**	387	81%	30						
Reflex response:									
General startle				[illegible]1		1.5		[illegible]8	
Blink reflex, etc.				59 4		54 9		64.6	
Discomfort, e g. crying				1.3	6[illegible]8	1.0	57 4	1 7	69 1

) The sound source was not fully usable until towards the end of the main investigation. It was relevantly presented only to 00 infants. Thus, the 73% do not regard the 440 infants of the column heading, but the 30% below By distance searching is meant that the box, when "wandering around the infant s body was kept at the distance of around 1 meter

) The sound source could not be hidden from the sight of the infant, and did not interest him.

) Other sources comprise sounds from a plastic tube, filled with lead pellets, two wooden rattles, a china can filled with lead shots, finger-clicking and handclapping, p M.10

Attempt at an estimation of a lower age limit [4]

As the test series applied in the main investigation had given no positive results before 2½ months of age for girls and 4 months of age for boys, an attempt was made to scrutinize the possibilities of finding the age reasons for negative results A random sample of 60 infants, having given negative results at a first testing, ranging between the age of 2.16 and 10 06 months and days at the first test, were subjected to renewed testing

The time between the first and the second test varied because of the difficulty to get the infants to appear at the WBC at an appointed time As is shown in table R.3 the renewed test gave in no case a positive result under the age of

Table R.4

The functions and the abilities of 87 Stockholm children examined in the follow-up of the main investigation after 2 years [6]

Items described in Methods, pp M.22—31

N = 87 distributed. 60 children > 2yrs <3yrs, 32 ♂ + 28 ♀

27 children > 3yrs <4yrs, 13 ♂ + 14 ♀

Functions and abilities, "free names	> 2 yrs < 2 yrs 6 mos				> 2 yrs 6 mos < 3 yrs				> 3 yrs < 3 yrs 6 mos				> 3 yrs 6 mos < 4 yrs			
	Pos.		Neg.		Pos.		Neg.		Pos.		Neg.		Pos.		Neg.	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Eye contact firm	4	7	3	1	17	18	8		8	9	1	3	3	3	0	0
1 Glance follows Teddy	3	7	4	1	14	17	11	3	8	9	2	2	3	2	0	1
2. Tower" building	1	6	6	2	9	13	16	7	5	7	5	4	1	1	2	2
Bridge building	0	1	7	7	6	12	19	8	6	9	4	2	1	2	2	1
3 Understand Color-Boat	5	6	2	2	13	13	12	5	10	9	0	2	3	3	0	0
4 Switch-back	7	7	0	1	19	17	6	3	9	11	1	0	3	3	0	0
Change feet	6	6	1	2	17	16	8	4	9	9	1	2	3	1	0	2
5 Pig-Board" pattern	0	0	7	8	4	6	21	14	7	6	3	5	2	3	1	0
6. Name pictures	5	6	2	2	16	17	9	3	10	9	0	2	3	2	0	1
7 Hiding-box	0	0	7	8	7	8	18	12	6	8	4	3	2	1	1	
8 Form-box	2	1	5	7	8	6	17	14	7	7	3	4	2	2	1	1
10. Pure tone orienting	1	0	6	8	8	10	17	10	4	6	6	5	2	2	1	1
Speech developed as communication means	6	8	1	0	20	20	5	0	9	12	0	0	3	3	0	0
Smile at the tester	7	6	0	2	20	18	5	2	9	8	1	3	3	3	0	0
Final judgment of communicative behavior	2	6	5	2	12	17	13	3	8	8	2	3	3	2	0	1

Table R.5

Associations between response behavior at testing of selective attention in infancy and communicative behavior respectively speech development after two years [4]

N = 87

Follow up in childhood after two years	Main investigation in infancy result									
	Head-turning after 4 of 5 sound presentat.			Eye fixation and eye contact with tester			Glance follows visual stimulus			N = 87 ♂ = 44 ♀ = 43
Functions and abilities:	φ	χ^2	signif.	φ	χ^2	signif.	φ	χ^2	signif.	
Eye contact firm	70	4_.64	0.01	44	16.74	0 01	.34	10.17	0.01	
Glance follows "Teddy	.03	0 08	0	_.4	5.00	0.05	43	16.05	0.01	
Understand instructions, Color Boat	.89	69 48	0.01	.5	.3 47	0.01	_.3	4 76	0.05	
Name pictures	.61	3_.1	0.01	.51	22.39	0.01	.53	4 04	0.01	
Adequate smile in tester s opinion	.35	10.4	0.01	46	18 05	0.01				
Speech normal" in mother s opinion	.35	10 63	0 01							
Speech developed at follow-up examination	45	17 71	0.01	.39	13 03	0.01				
Sociability at follow-up examination	40	14 06	0.01							
Change feet in stair case (cf e g. Bühler and Hetzer*)	.54	25.28	0.01							
Understand instructions, Tower (cf Terman-Merrill/Hellström* Gesell* *)	.81	56.93	0.01							
Manage Tower" and Bridge building (cf ref.former item)	.56	7.65	0.01							
Final judgement of communicative behavior	41	14.85	0 01							

) as a means of communication, cf p I.1

Table R.6

Follow-up by correlations with the "4 years-of-age check-up" [4] [6] [7]

N = 51 ♂ = 25 ♀ = 26

The main investigation:			/— —/	/— +/	/+ —/	/+ +/	Total	φ	χ^2	Signif.	N =
Sound attention manifested in 4 head-turnings after 5 presented sounds	correlated with	Follow-up after 2 years	17	6	1	27	51	73	27.36	0.01	51
		boys	9	4	1	11	25	.62	9.64	0.05	25
		girls	8	2	0	16	26 51	.84	18 49	0.05	26
		4-years-of-age check-up of hearing	3	20	1	27	51	18	1.57	0	51
		4-years-of-age check-up of sight	3	20	3	25	51	04	0.07	0	51
		4-years-of-age check-up of speech	12	11	3	25	51	45	10.45	0.05	51
		4-years-of-age check-up at psychiatr examination	11	12	2	6	51	46	11 00	0.05	51
Eye fixation at the main investigation correlated with		4-years-of-age check-up of sight	4	9	2	36	51	.35	6.07	0.05	51
Communication at the main investigation correlated with		Follow-up study	10	3	7	31	51	.54	14 9	0 05	51
Follow-up after 2 years total result	correlated with	4-years-of-age check-up of hearing	3	15	1	32	51	.24	3 00	0	51
		4-years-of age check-up of sight	3	15	3	30	51	11	0.64	0	51
		4-years-of-age check-up of speech	13	5		31	51	69	24.56	0.01	51
		4-years-of-age check-up at psychiatr examination	10	8	3	30	51	.51	13.24	0 01	51

Table R.5

Associations between response behavior at testing of selective attention in infancy and communicative behavior respectively speech development after two years [4]

N = 87

Follow up in childhood after two years	Main investigation in infancy result									
	Head-turning after 4 of 5 sound presentat.			Eye fixation and eye contact with tester			Glance follows visual stimulus			N = 87 ♂ = 44 ♀ = 43
Functions and abilities	φ	χ^2	signif.	φ	χ^2	signif	φ	χ^2	signif.	
Eye contact firm	70	4..64	0.01	44	16.74	0 01	.34	10.17	0.01	
Glance follows Teddy	.03	0.08	0	..4	5.00	0 05	.43	16 05	0.01	
Understand Instructions, Color Boat	.89	69 48	0.01	.52	..3 47	0.01	..3	4 76	0.05	
Name pictures	61	3...1	0.01	.51	22.39	0.01	.53	4.04	0.01	
Adequate smile in tester s opinion	.35	10 42	0.01	46	18.05	0 01				
Speech normal" in mother s opinion	.35	10.63	0.01							
Speech developed at follow-up examination	45	17 71	0.01	.39	13 03	0.01				
Sociability at follow-up examination	40	14.06	0.01							
Change feet" in stair case (cf e.g. Bühler and Hetzer")	.54	..5.28	0 01							
Understand instructions, Tower" (cf Terman-Merrill/Hellström" Gesell"")	.81	56.93	0.01							
Manage Tower" and Bridge building (cf ref.former item)	.56	"7.65	0.01							
Final judgment of communicative behavior	41	14.85	0.01							

) as means of communication, cf p 1 1

COMMENT ON RESULTS, ACCESSIONAL FINDINGS, AND CONCLUSION

Additions to the main investigation [4]

Methodological aspects were considered to call for a trial to find out what conditions, external and/or internal might influence the possibilities of examining selective attention in infancy with the applied equipment.

Influence of external disturbances [4]
By comparing the responses of infants, having had a polio vaccination shot shortly before the examination, with responses of the other ones, this analysis was regarded as being carried to its extremes. Thus, pain was supposed to give rise to a perception, more dominating than e.g. background noises, cf Luria et al.[112] Even though a small number of infants injected before the examination, were found the following comparison was undertaken.

Table C.1
The significance of a polio vaccination "shot as disturbing the selective attention in infancy [4]

Total population N = 479 ♂ = 264, ♀ = 215
Shot" given bef. N = 52, ♂ = 31 ♀ = 21
No shot" before N = 427 ♂ = 233 ♀ = 194

Final result regarding selective attention		Polio vaccination shot before testing of selective attention: —	+	Total	φ	χ^2
	+	333	41	374	.01	.02
	—	94	11	105	Significance	0
		427	52	479		
Percentage of negative final judgments		22.0	21.[illegible]			

There was no significant association found between negative results and "shots" In 427 infants not injected before the examination, there was about the same percentage negative responses [22.0%] as in 52 infants having had an injection before the examination [21.2%]

No final conclusion was drawn, as the distribution was regarded as being skewed, but the presumption was ventured that a test of selective attention can be performed at relatively disturbed conditions The memory span as to perceptual experiences appeared to be short, even regarding pain of the shot type

Influence of social conditions [4] Among social conditions, the milieu factor of family size was regarded as interesting. The comparison had to be restricted to firstbirths and infants with one or more elder siblings.

Table C.2
The significance of sibling order regarding final result of selective attention testing in infancy [4]

Total population	N = 45..	♂ = .53	♀ = 199
First births	N = 308	♂ = 168,	♀ = 140
Second	N = 114	♂ = 68	♀ = 46
Third	N = .2,	♂ = 13	♀ = 9
>	N = 8	♂ = 4	♀ = 4
(Twins, stillborns, miscarriages	N = 15	♂ = 6,	♀ = 9) cf table S.5

		First births ≧ Second births				
Final result regarding selective attention		—	+	Total	?	χ^2
	+	254	104	358	12	6._5
	—	54	40	94	Significance	
		308	144	45[illegible]	at 0.05 level	
Percentage of negative final judgments		17.5	77 7			

There was a significantly higher percentage of negative responses in the population of higher sibling order No definite conclusion has been drawn from this outcome since the selection of families from the inner center of the city has not been analyzed more closely The differentiation of sexes has been felt irrelevant because of the small groups with higher sibling order

It has been regarded as extremely difficult to judge about social conditions, as illustrated by the distribution of occupations in table S.2. Today vocational status no longer reflects differences in the care or upbringing of infants.

However the social situation of being alone with an infant was considered as a difference calling for a calculation of possible associations regardless of marital status Thus, around 15% of the mothers were not living together with the fathers of the infants. There was no significant association found between a neg-

ative final result of the examinations and the social condition of being alone with the infant as shown by the values of

$$\chi^2 = 3.68 \text{ and } \Phi = .09$$
significance = 0 (N = 449)

This result should not be over-interpreted since it has not been possible to make a distinction between negative results due to psychomotor immaturity and/or eventual social deprivation*

There is a strong positive association between good physical care as reported by the WBC-nurse and a positive final result of the selective attention examination. This correlation has only been possible to compute regarding 455 infants since the conditions were not known to a desirable extent for all infants The correlation, therefore, should not be over interpreted. The values were

$$\chi^2 = 29.22 \text{ and } \Phi = .25$$

significant at the 0.05 level (N = 455)

The influence of social conditions has not, in this study been analyzed sufficiently to draw conclusions A larger population would have been required as well as a less spread out distribution of ages. Since the purpose of the study has been quite a different one the figures are left here only as an information for eventual future research in the field of social deprivation in infants.

Table C.3

The significance of lacking articulation regarding final result of selective attention testing in infancy [4]

Total population N = 473 ♂ = 63 ♀ = 210

		No articulation –	No articulation +	Total		
Final result regarding selective attention	+	233	126	359	16	12.38
	—	46	55	101	Positive association at 0.01 significance level	
		279	181	460		
Percentage of negative final judgments		30.3	16.4			

Column headings at the right of the table: ♀ (above 16) and χ (above 12.38).

Finally the cooing and articulation were correlated to the outcome of the main investigation, as an influence of functional status.

Among infants with no vocalization or failing articulation the negative responses are 30 % and among vocalizing or articulating infants 16 %

The notations of status presens referred to at p M.16 concerning e.g. the infant's type of cooperation are shown below with the reservation that—lacking reference basis—they should be regarded as a subject of discussion concerning future methods for testing small infants, and nothing more.

Table C.4

A tentative comparison between functions and selective attention as tested with the methods of the main investigation (4)

N = 480 ♂ = 265 ♀ = 215
N = 375 ♂ = 204 ♀ = 171
N = 105 ♂ = 61 ♀ = 44

Final result of main investigation regarding selective attention		Positive	Negative	Total	φ	χ^2	Signific. level
Attention							
As noted under status presens	+	301	74	375	.48	109.30	0.001
on protocol card fig M-9	—	-8	77	105			
Orientation							
As noted under status presens	+	145	-30	375	11	11 44	0 01
on protocol card fig M-9	—	60	45	105			
Eye contact fig M-9							
As noted in anamnestic information:	+	3[illegible]7	48	375	.0	16	0
Eye fixation early as reported by the mother	—	90	15	105			
Eye contact and eye mobility as	+	61	1	[illegible]	.34	39 09	< 0.01
checked by the tester cf glance follows"*	—	40	-3	63			
Interest							
As noted under status presens	+	-28	147	375	.09	3 60	0
on protocol card fig M-9	—	53	5	105			

*) Eye contact, as checked by the tester" has been computed only in case of satisfactory psychomotor maturity in the infant, which means that no infants have been taken into account belonging to an age category when a failing neck-and-back stability can be regarded as normal, i.e. no girls under 4½ months of age, and no boys under 5½ months of age. Therefore, the computation comprises only 345 infants, thus judged:

Total population	N = 345 ♂ = 187 ♀ = 158
Eye contact exists	N = 301 ♂ = 165 ♀ = 136
Lacking eye contact:	
no following response	N = -5 ♂ = 15 ♀ = 10
No fixation and/or	
slow and distracted	N = 19 ♂ = 7 ♀ = 1

The positive association between the negative outcome of an examination in infancy and a lack of eye contact has been taken highly into account when the methodological aspects of a selective attention screening have been considered, cf p D 15

It should be observed that the orientation part of the behavior accounted for above was dichotomized thus. Orienting capacity cannot be established and Orienting capacity has been established which means that the possibility to differentiate between negative responses due to psychomotor immaturity and psychomotor deviations, respectively has been unsatisfactory

Practical adaptability of sound sources [4] have to be reported by additional comment, since the graphs, showing response distribution, figs R.1—7 and table R.1 fail to inform about the usability of the applied methods. The experience during the investigation resulted in the following considerations

Although the *rattle* got the highest number of presentations, table R.1 the sound source was inferior to the bell. It did not have the same ability to maintain the interest of the infant, which was especially obvious when it was moved around the body

An extra hand movement was required to produce the sound, which meant a risk of a possible response to visual stimulation when the sound source was moved. Even so, not a single infant attempted the searching response in the meaning that head and glance followed the movements of the sound in an unequivocal fashion. This was interpreted as the rattle sound being less attractive than the bell sound. Fig C.1 compares the sounds irrespective of searching responses.

From the protocol it appears that there were 109 of the 312 infants who responded to the *bell* sound—without any sign of fatigue—by searching for the sound when it was moved around the body as well as by the ordinary head-turning. This cannot be illustrated by the graph, though.

To give a correct picture of the *bell* as sound stimulus, the searching response ought to be added to the result twice.

The search for the sound begins at a later age than the mere head-turning. It calls for an upright position and a manifest steadiness of muscles and movements. A comparison with the total number of infants more than 4 months old shows that, in all, around 35% searched for the bell sound. The ordinary head-turning responses started as early as about the 3 months level.

At the age of 5 months scarcely 25% of the positively responding infants searched at 6 months almost half of them, and later on about 80% Possibly the searching response provides a more certain basis for the assessment of selective attention behavior but the technique requires much insight and experience

As to the *Montessori sand-cylinder* even up to the age of 8—9 months still about 30% of the infants gave negative responses, although responding positively to most of the other sounds. The complicated presentation was also regarded as a disadvantage

Since the *stopwatch* called for the

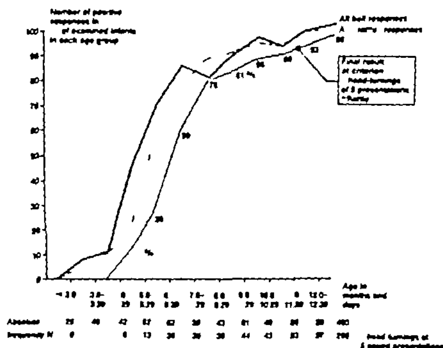


Fig C.1
Comparison between the two sound stimuli presented the highest number of times and all sound stimuli at the criterion of 4 head-turnings after 5 sounds both sexes (4).

participation of the mother it required too much time and was considered less suitable as it also showed a lower response percentage moreover starting at a higher age level (cf also fig C.3) than for instance the bell.

No definite conclusions have been drawn from these statements, but for the suggestion that the sound of fine sand on a wooden surface as well as stopwatch ticking may call for a more advanced maturity stage than percussion sounds of e.g. the rattle and the bell type

The comparison between the "*cradle*" and the *bell* shows a difference which is inexplicable The presentation methods of the two sound sources are equally handy In a similar way as was done with the *bell* the "*cradle*" could be moved around the baby's body since it was quite possible to make it emit sounds with extremely small hand movements, and it could be fairly well hidden in the hand Still, the percentage of positive responses was remarkably lower than that of the *bell* The conclusion drawn was that this

was due to different ability to interest infants. The *bell* appeared to be more attractive.

Furthermore the response percentage on the sound stimulation of P_1 P_2 and Pl does not tell about the practical difficulty of presenting the paper and plastic-*crushing* unnoticed by the infant's vision. Since the *paper* or *plastic* had to be compressed lightly about 20 cm directly behind the ear of the infant, and the size of the *crushed paper* often called for the unprepared assistance of the mother unexpected complications were caused.

As the mothers usually had to be convinced that the sound of the crushing existed* the tester first crushed the paper at the proper distance directly behind the mother's ear before an acceptable participation could be obtained. Thus, the infant had time to have his attention diverted, and the visual contacting procedure had to be renewed, before the sound was presented again.

Even though the *mini-music box* was not fully used until the end of the investigation, it was obvious that it, without exception captured the infant's interest to the highest degree of all the sound sources. However the comparatively low percentage of presentations were, to a greater extent, caused by no presentation than by failing positive response The conclusion was that the presentation technique calling for much speed and nimbleness, did not suit conditions including limited time. Furthermore, no response was obtained under the age of 4 months.

Finally *whispering* from behind was found to be an important contribution to the final judgment of selective attention behavior although it places considerable demands on the tester and the environmental factors The tester has to have access to space fig C:2 Instructions to the parents must be given quickly and quietly The tester should also have experience regarding the signification of sound intensity cf fig P.2 and Sheridan[148] The parents' ability to comprehend must be taken into consideration.

Comparison with Griffiths' baby test [4] The lack of Swedish reference basis motivated the comparing of results with some of Griffiths' sub-tests in her Mental Development Scale for Testing Babies from Birth to Two Years [69] Including locomotor development* in in-



Fig C:2
The final whispering takes place when the baby is leaving
Photo Mats Dedrik Bellander

) Now standardized for Swedish infants by Lindstam[78]

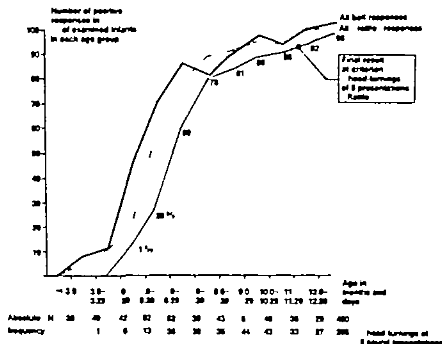


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Fig C.2
The final whispering takes place when the baby is leaving
Photo Stan Dedrik Bellander

) Now standardized for Swedish infants by Lindstam[10]

fants 3—9 months old, the items offer the closest reference available although not directly comparable. Neither the purpose of Griffiths study preceding her standardization of the scales, nor the presentation method did coincide satisfactorily.

Griffiths has a total of 571 infants, aged between 1 and 24 months, divided into about 20 infants for each month. The procedure is revealed by the headings under fig C.3 but nothing is told about visual contact initially established, before listening to the tuning fork, or at what distance the stopwatch is to be held etc.

Griffiths subjects in the age category of 4—9 months are shown at p C 9 to-

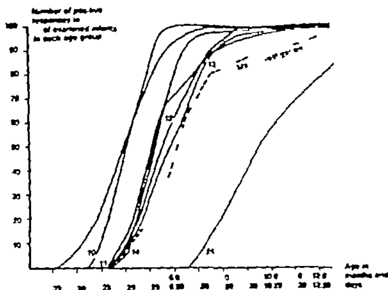


Fig. C.3
Comparison between 7 speech and hearing items from Griffiths[*] and the result from the main investigation [4].

Griffiths' curves:
9 Searches for sounds with head movements
10 Laughs aloud
11 Turns head deliberately to bell
12 Listens to tuning fork
13 Coos or stops crying on hearing music
14 Talks (babbles) to persons
24 Listens to stopwatch

gether with the infants of the main in vestigation [4]

Age in month	Griffiths*	Main investigation
IV — VI	79	156
VII — IX	71	133
Total	150	89

Fig C:3 should only be regarded as presenting common trends well known to researchers in the field of communicative development, but it is also an argument supporting the judgment of the stop-watch being a less suitable aid for the purpose of early attention testing.

Although Griffiths plateau-formations as a whole commence at earlier levels than those of the main investigation, the item 11 turns head deliberately to bell coincides strikingly well, fig C 4

Comment on the clinical calibration [5]

The difference in examination conditions should be considered when an unconventional method like the clinical calibration of the sound sources is to be evaluated. Schoolchildren have more hearing maturity than infants under one year of age.

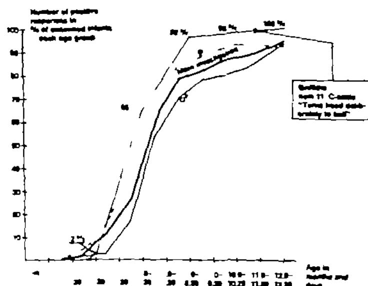


Fig C 4
Result of main investigation at the criterion of 4 head-turnings in 5 presentations, compared to Griffiths item Turns head deliberately to bell" [4].

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Griffiths subjects in the age category of 4—9 months are shown at p C-9 to-

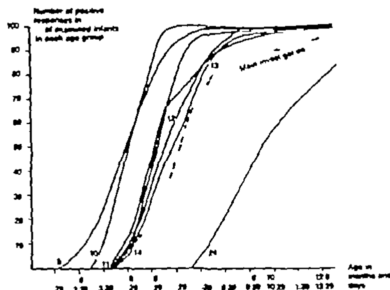


Fig C.3
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13 Coos or stops crying on hearing music
14 Talks (babbles) to persons
24 Listens to stopwatch

municative disorders should include those caused by organic hearing loss the selective attention test should comprise complex sounds covering the following claims:

The fundamental tone should be placed somewhere above 4 000 Hz. Its intensity maxima should not exceed the level of 40—45 dB in free field, assumed that the presentation take place close at hand, within arms length's space

Furthermore they should possess as much attractiveness to babies as do the rattle the bell and the mini-music box. However they should be as small, easily handled and invisibly adaptable as the jingle bell.

Follow-up—additions and comment [6]

Sources of error possible at the selection of subjects [6] The positive associations stated between the outcome of the main investigation and the follow-up after two years have to be commented. Thus, the possibility of errors may be hidden in the selection of subjects In the main investigation the number of infants motivating a closer study was lower than that of the follow-up concerning 29 of 87 children.

The reason why parents accept summonses to a voluntary examination is difficult to penetrate Some parents may have been anxious for the speech development and/or the hearing of their children. On the other hand, some parents may react in the opposite way An anxiety because of a questionable section of the child's development may make them unwilling to come, because they cannot help being afraid of getting their suspicions confirmed. Within the routine of the well baby clinics the staff is familiar with different parental attitudes regarding summonings.

Since the purpose of the follow-up has been a methodological one, however the selection of follow-up subjects is of minor importance. All the examinations took place without checking with the results of the main investigation and the aim was not a diagnostic one, but to look for the predictability of a method.

Critical considerations [6] The positive association between Eye fixation and eye contact with tester in infancy and Eye contact firm in childhood should not be astonishing. The still much stronger association between the final result of the selective attention examination and eye contact at the follow-up appears to emphasize the necessity of a firm eye contact having been established and checked in a screening procedure

Among all functions judged about in the tables R.4 and R.5 the Eye contact firm" has the key position. Since there was no blind or severely sight impaired child participating in the follow-up study no child with a negative marking for eye contact was given a positive marking as a final judgment regarding communicative behavior

The lack of association between the final result of the main investigation and the item Glance follows Teddy calls for the complimentary information that many children appeared to be entirely uninterested in Teddy although the initial eye contact with the tester had been good. The item was possibly an unsuitable one.

The remaining items in table R.5 are all of immediate influence on communicative behavior but for the "Change feet in staircase"

The Color Boat item thus, calling for the understanding of an analogy shows a strong positive association on the 0 01 significance level, as well as "Name pictures and "Build Tower" It should be mentioned that the items "Change feet in staircase Tower" and Bridge building, all correlating positively with the result of the main investigation, are included in available psychological tests for young children at the 3 years of age level.

The correlation with "sociability on the examination has been interpreted as a further confirmation of the assumed 2 years prediction.

Speech development of the followed up children [6] Although the prediction value of the testing methods was the main purpose of the follow-up it was also given the secondary aim mentioned at p M.25 Thus, it was felt desirable to utilize the opportunity of getting a linguistic description of the speech development in a population of Stockholm children around the age level of 3 years No investigations have been undertaken regarding Swedish children, concerning the first phase of the speech development, which should end at 4 years of age according to e.g. Erasmie[60]

Since this description is tentative it should not be regarded as a formal result, but a contribution to a discussion on trends in Swedish speech development. It is reported in Appendix I table A.2, Phonetic realization of Swedish phonemes, grammar and semantic ability in 87 Stockholm children Dealing with the Swedish language this survey is available only in Swedish.

The schedule made by the speech pathologist followed the norms of Sabbatsberg s phoniatric clinic regarding the ability to differentiate the linguistic material from a phonematic and a semantic point of view The realization of vowels, consonants, and clusters was noted Sentence-building was reported as well as prosodic characteristics Perseveration was observed The smile was noted

As could be expected, the phonetic realization of the phonemes were a function of age Articulatorily the most unexpected deviation was the difficulty which the vowel-phoneme /ɵ/ of the Swedish word hund" offered. Most common was the substitution of /ɵ/ into [ɔ]. Fricatives as /s/ /ç/ /ʃ/ were substituted. With one single exception, supradentals were not at all present.

Further it was an exception that any of the followed-up children could connect a pronounced name of a color with an object of this color or name the color himself spontaneously The ability to identify colors by matching them on the other hand, was prevalent even in the youngest children. The capacity of color identification has deliberately been noted separately in Appendix I, table A.2.

It should be remembered that the examinations took place without checking with the results of the main investigation in advance. The analysis of the manifested speech caused by the comparison with the main investigation the following observa-

tion. The deviating phonetic realization of phonemes and/or linguistically poor communication with remarkably defective speech appeared to be connected with sound attention response in infancy No formal correlation is made, but no child with negative markings for speech development and communication in table A.2 was found to have a positive final result at the criterion of 4 head-turnings of 5 presentations in infancy This information should not be delivered as a formal result, but as a subject for debate, and for further research.

Evaluation of prediction [4][6]

Non-correspondent results of the main investigation and the follow-up The check with the main investigation after the end of the follow-up showed that 25 of the 29 children, judged as negative at the final judgment of communicative behavior had given rise to negative results also in infancy However the reason why was noted regarding 9 of them, being too young This necessitated an attempt to compute the influence of the infant's age on the association. Thus, regardless of age the association is expressed by the values of

$$\Phi = 0\ 41 \quad \chi^2 = 14.85 \ (N = 87)$$

showing significance at the 0 05 level, which means that the predictability until 2 years later is significant.

If the 9 subjects be removed a much more accentuated positive association is obtained, though, expressed by the values of

$$\Phi = 0\ 75 \quad \chi^2 = 48\ 72 \ (N = 78)$$

showing significance at the 0 01 level.

Another point of departure could be chosen, however Referring to the limited follow-up of 60 infants reported in table R.3 and at p R.9 it could be reasonable to remove all children being less than 5 months and 12 days on the main investigation. The following positive association, thus, is achieved

$$\Phi = 0\ 41 \quad \chi^2 = 9\ 68 \ (N = 59)$$

showing significance at the 0 05 level

Finally a fourth suggestion could be discussed. If all the infants judged as too young were removed from the entire follow-up, irrespective of the results being positive or negative the following association would show

$$\Phi = 0\ 41 \quad \chi^2 = 14\ 79 \ (N = 62)$$

showing significance at the 0 05 level.

The conclusion will be that the final result in infancy correlates with the final judgment of communicative behavior in childhood, thus giving evidence of the predictability of the method used for examination of selective attention.

Comment on non-corresponding cases [4][6] The 7 cases which showed a non correspondence between examinations in infancy and 2 years afterwards are distributed like this 3 cases had negative markings in infancy and were judged as positive in the follow-up and 4 cases judged as positive in infancy had negative" final judgment after 2 years.

One child was in the protocol from the main investigation, noted as an adoption case At the time of the infant examination the child came practically directly from an infant nursery home, a milieu which may sometimes represent a more

or less "poor" communicative stimulation[1 8,12, 1] At the *first confrontation* at 9 months of age, the infant was judged as follows delayed development easily distracted uninterested in contact."

At the follow-up examination the child showed a completely normal development and a very well managed speech ability The adoption home probably had been rich in stimulance The parents appeared to be anxious to do their best to contribute to the general development of the child, whose sociability was striking.

The second child noted negative" in *infancy was found to have been hospitalized* at the time for the first examination In the past history notes stomach pains were mentioned which had made the infant serious and transparent

Although the third child had been considered as somewhat delayed both on the main investigation and at the follow up there appeared to be no other explanation regarding the "negative response but the injection the infant had received shortly before the test. Although no significant influence has been found due to shots cf p C.1 there should evidently elapse a due time between shot and test. The protocol from the main investigation states only Difficult to say why response does not appear Ought to respond. The shot?

Of the 4 remaining children judged as positive in infancy and negative 2 years later one child was aged 8 months and 27 days on the main investigation. In the past history the mother was characterized as slow lacking contact, unrealistic The follow-up reported. nervous bites his nails to the root, looks anxiously at the mother and the *tester as if uneasily worrying about doing* something forbidden Does not seem interested in speech learning. Says 'yes/no wrongly says only a few words no sentences. Keeps saying [het:]. Motoric reactions slow serious, frightened "

The second child had a much distorted phoneme-realization and abberating articulation all along the line The mother reported Panic in front of new people, delayed speech, unconcentrated laughs in the wrong place." Furthermore, the child was said not to pay attention to admonitions likes to be a disturbance, etc."

The third child had been accompanied by a "day mother taking care of the child during the day when the mother was at work. This "day-mother had incomplete information as to the case history In the well-baby clinic s report there were found notations regarding the child having suffered from early otitis and having been hospitalized The follow up examination says " gives an impression of contact difficulties Rejective and sullen. Lacks eye contact. Says only *a couple of words, silently and unkindly*

For the fourth child, finally the follow up study notes Had otitis 4 times. Does not want to look up Keeps sitting with hands before his eyes. Does not want to play with strange children, says mother Baby-like motoric pattern. Destructive. Wants to tear everything down. Kicks and beats mother Mother urges child to stand with his back to tester not looking at her

Three of the described children, regarded as normally behaving at the infant

examination, were nearly 9 months old when first examined—one was practically 10½ months It is possible that an ex amination earlier at the 7 months old level, could have given an indication that a renewed examination be suitable It must be kept in mind that, even though an early sound attention test, according to the present study is recommendable to be included in the routine of the general health program, the *continuous milieu in* fluence on children s development has to be taken into account.

Comment on the 4-years-of-age check up As expected, the small number of examined children does not allow a cor relation to be computed regarding sound attention in infancy and hearing at 4 years of age The population is too skewed, and the following fact gives the evident ex planation.

The number of hearing impairments, important to speech aquisition, is 1—2 for 1 000 children at the age level of 7 years. For the first year of life the frequency is unknown. For many reasons, however it is a smaller number than that of the children 7 years old. Many hereditary hearing impairments have shown a tendency to deteriorate during the first years of life, cf Barr and Wedenberg[8] They may remain unnoticed during infancy and show first in the school situation, at 7 years of age In the statistics of this age group there are also organic hearing defects present, due to many exogenous factors including e.g. meningitis occurred during infancy

The probable frequency of children with congenital hearing defects could be 0 05 to 0 1 percent at the newborn age level. For obvious reasons, thus none of the 480 infants of the main investigation or the 51 children of the 4-years-of age check-up appeared to be hard-of-hear ing so severely that the speech development risked an impediment.

Of the 47 children, with normal hearing at the 4-years-of-age check-up 27 re sponded positively in infancy with 4 head-turnings after at least 5 sounds, 15 responded after less than 4 sounds, although their responses to the bell sound and the mini-music box as well as the cradle were positive, and 5 were judged too young" Of the 4 remaining children 3 were negative both in infancy and at the check-up, even though this did not appear to be due to organic hearing loss. They were referred to as observation cases, probably mentally retarded The fourth child had been judged as positively responding in infancy and did not cooperate at the 4-years-of-age check-up No more notations were found, only that the child had moved out of the district. Thus the non-cooperation could not be analyzed.

Approximately the same conditions influence the correlations of visual func tions, even though there could be achieved a basis for computation of associations between Eye fixation in the main investigation and sight control at 4 years of age The same 3 children who were ne gative at the hearing examination did not cooperate at the sight control either They were referred to as probably mentally retarded. The positive association obtained is shown in table R:6

A complete follow-up with 4-years-of-age check-ups could have meant a

most valuab e prospect for the judgment of the prediction quality in the methodological design of an attention test intended for mass screening in infancy had it only been possible to fulfill it

Conclusion [4][6][7]

According to the questions raised at pp I 2—I 3 this study has given rise to the following conclusions

a) Response to sound stimulation should be manifested by the distinct head-turning in the direction of the sound source after initial diversion of visual interest. Although sound attention is present from shortly after birth, the response behavior is not differentiated during the first three months The lowest age level for the screening of selective attention ought to be 7—8 months

b) Consistent difference in selective attention in infancy is caused by the sex difference Girls respond approximately one month earlier than boys to sound attention tests when presented with the methods applied in this study They furthermore show a higher percentage of positive responses within each month age level.

c) The predictability of the method applied has been shown regarding communicative behavior two years later

d) An initial firmly established eye contact and a check up of visual attention by an attractive object, held in front of the infant s eye, preceding the sound presentation is a necessary prerequisite for a screening test of selective attention An interest arousing sound stimulus, easy to handle invisibly should not have any frequency component below 4 000 Hz, and the sound pressure level should not exceed 40—45 dB

DISCUSSION

The need for an early communication screening [8]

No infant should miss the opportunity of a stimulance which could further his communicative development. However it cannot be expected—or desired—that communicative disorders be traced by a general psychological testing of all infants. The shortage of specialists is too evident. More simple methods for screening should be searched for

Although society has long devoted efforts to solving the problems of early detection regarding many disorders the emergence of language function has often been subjected to a policy of wait and see Regarding the organic hearing defects, Wedenberg[171] Holmgren[87] and Barr[3] have played a pioneering and leading part. Bearing in mind how thinly spread out the population is and how large the distances in our country are their program for early training and follow-up of hard-of-hearing children is remarkable A highly desirable goal would be to create related programs for other types of communicative disorders as well.

The concentration upon risk groups sometimes suggested as the adequate form of screening, does not offer all infants a full guarantee of early detection so that they can get the educational stimulance *desired and good support. Since the risk* usually is identified by known conditions, potentially interfering before during, or after birth and caused by accidents, diseases hereditary factors, or otherwise, there is always a possibility that severe mental and/or emotional communicative disorders too long remain undiscovered because they hide behind a misleadingly normal appearance

A more realistic and fruitful point of departure would be to concentrate efforts upon a simple screening within the frame of the child welfare program. In case of imperfect communication, even after renewed testing, a referral to specialist examination in the child clinics of the hospitals would be recommendable besides other suggestions regarding stimulance and training at a home basis This study presents a program of this type with the BOEL attention screening test, pp D 5 [8]

As the great majority of Swedish infants are under continuous supervision of their physical health during the first year of life, observations made at that age level

during the course of a rapid screening would mean a more safe guarantee for the early detection of communicative disorders, irrespective of their belonging to risk groups

There are many suitable opportunities to fit such a screening into the health program without requiring extra staff or additional summonses The aim of using a method like the one reported would be that it is simple and inexpensive

For the demand of a mass screening in infancy there is no need for a pure tone generator e.g. an audiometer or a sound proof room.

The sounds used should in the first place have the "news value" for the infant, causing him enough curiosity to let him leave an attractive visual stimulus which has caught his initial interest and attention Informal complex sounds should be produced by tools having the quality to be easily and invisibly handled by one person, preferably the WBC nurse. If this screening be made a routine, the WBC-staff as well as the parents would get more used to observing the important communicative ability in infancy

The method applied gives, moreover if all its resources are utilized the by-product of informing about general development and behavior Its basic demand for a firmly established eye contact is not only showing the infant's ability to give priority to incoming signals selectively but forces the examiner to observe e.g. the symmetry of the eyes, their mobility the general hand function and the ability to grasp Such an important detail as the smile[2, 21] is reported.

If the results presented in fig. C.1 be literally interpreted it is to be expected that between 15—20% of all 7—9 months old infants be placed in a category of "cases for observation It would appear to be "worthwhile" to repeat the testing, in case of negative response provided that the renewed testing does not take place when the infant is more than 10 months old

Communication nomograms —a prospective aid to health check-ups—with sex differences considered

On the basis of age levels for manifest selective attention it ought to be possible, as a guide for future health check-ups to construct a normative scheme for communicative behavior analogous to current nomograms regarding weight, length, ability to sit, grasp, crawl, walk, etc. cf e.g. Griffiths[60] Gesell[64] Hagberg[74] There is a field open for further research and development.

Why should a communication quotient" not be as useful to diagnosticians and educators as the IQ since the social ability of communicating has such a key position for the child's future adjustment, emotionally as well as intellectually? This should be taken into account to a larger extent in the child welfare program The ability to communicate is a main part of the health, to the infant as well as to the child growing up

Both regarding a "communication nomogram and a quotient it is important that the constructor considers the sex difference found in this study Assumed that it is valid even for a larger popu-

lation, both parents and other people in charge of infants should be aware of the fact—statistically speaking—that it is unreasonable to expect the same performance level from boys as from girls

Even though there is already a general awareness of boys being later developers than girls some correction factor concerning sex differences ought to be included in tests involving communication ability Obviously we risk being unfair to the boys, maybe also with regard to the rate of development of other abilities than those dealt with in this study

Current baby and infant tests*[8, 10, 27, 42, 49, 110] present their testing scales without distinguishing between male and female children by a formally computed correction factor Lindstam[11] in her Swedish version of Griffiths Mental Development Scale for 0—2 years available after this study was finished, has pointed out that a significant difference between boys and girls exists during the second year of life. She found a significant difference regarding the B- C and D-scales and makes the following comment:

As to personal-social behavior and language behavior the results of girls are definitely better than those of the boys — — — The superiority of the girls in verbal tests can be shown already during the second year of life Their better results at the B- and D-scales may be assumed to be due to some general contact factor which has appeared in the form of a greater preparedness to cooperate in the test situation (pp 25—26)

Other investigators also have found sex differences during—and after—the second year of life. Klackenberg-Larsson and Stensson report in Karlberg et al.[?] "Significant differences between the sexes in favour of girls are present from 18 months to 3 years most marked at 2 years Girls are more advanced particularly in the language and social sphere." (p 90)

The findings of sex differences also during the first year may be considered further Although the general view of the sex differences is repeatedly provided for by parents and educators more research is desirable with respect to factors other than speech.

Hand motor development rate [4] A trial to further elucidate the sex difference is shown in table D-1 and fig D-1 As there was found no difference in the locomotor and performance scales in Lindstam's[110] comparison by Griffiths'[49] scales (above) the following comparison was felt to be of interest.

The table shows Griffiths age limits regarding the onsets of different abilities and the subjects of the main investigation are placed within these limits. Since the main investigation did not comprise an unequivocal distinction of grasping ability the table and the figure should not be literally interpreted, but regarded as demonstrating a trend subjected to discussion. The viewpoints may appear marginal, but since the handgrip is to be reported at the BOEL testing presented below they were intended to give additional information of some importance.

*) Concerning personal-social, hearing and speech, etc and hand development.

Table D·1
Some approximate data on hand motor development from Griffiths and the main investigation [4]

Ages adapted to Griffiths grouping	Cannot grasp stick		Directs hands and starts grasp		Grasps and puts into mouth		Well develop. grasping with pincers grip		Deviating hand motor development		Total N	
Months	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
3 and 4	39	30	12	10							51	40
5 and 6	4	1	30	28		3					54	43
7 and 8			3	4	31	32					38	36
9 and 10		1			39	29		10	1		4	4
11 and 1					27	5	8	[illegible]	1	1	36	6
N = 408	67	43	45	4	97	69	8	30	4	3	221	187

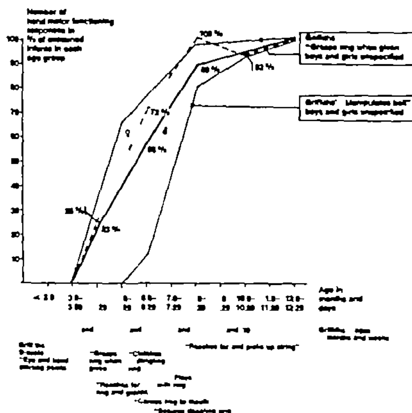


Fig D·1
Comparison between hand motor development as shown by Griffiths and the main investigation [4].

The graph does not show a difference which is clear from the table. The well developed grasping with pincers grip has appeared earlier in the girls examined in the main investigation than in the boys. The compared groups are small, but still it is interesting to see the trend being the same as for the testing of selective sound attention.

The BOEL attention screening test for infants [8]

General considerations When the decision was made to utilize the experience and findings from this study for the development of a simple screening equipment, the constructor was well aware of the necessity to reduce the number of sound sources in order to make the method more practically adaptable to the routine of the WBC program. The essential information requested—being the ability of the infant to focus his attention—ought to be obtainable by a less demanding response criterion.

The decision to prefer the bell type of sound source is evidently explained by the results table R.1 and figs R.1—7 and the comment on practical adaptability pp C.5 The prospects of the sound source reduction called for a study of associations between the follow-up and the outcome of the main investigation at the criterion of <4 head-turnings. Thus, positive responses to the bell and the rattle as manifested by distinct head-turnings were associated with the items.

	(N = 87)	*correlation*		*sign. level*
sociability at follow-up,	*showing*	$\varphi = 41$	$\chi = 14\ 49$	$p = 0.01$
speech developed		$\varphi = .33$	$\chi = 9.27$	$p = 0.05$
Name pictures		$\varphi = 42,$	$\chi^2 = 15\ 44$	$p = 0.01$
Understand instructions		$\varphi = 41$	$\chi^2 = 14.94$	$p = 0.01$

The associations found were interpreted as a support to the reduction of the sound sources to two Some further correlations were made regarding infants who had responded only to the bell and/or the rattle considered to be illustrating communicative qualities They are shown in table D.2 and deliberately presented as a subject of discussion.

However the associations are of interest because the BOEL test presented below includes reports regarding smile.

Finally the formal positive result of distinct head-turning to bell and rattle* associates with the formal positive responses at the items of the follow up, thus.

$$\phi = .58 \quad \chi^2 = 29.24 \ (N = 87)$$

correlating positively at the 0 01 significance level. On the basis of this finding two sound sources were decided upon.

BOEL s relative independence of surroundings The short time span for a BOEL attention test calls for a thorough

Table D.2
Association between communication in infancy and childhood as manifested by communicative responses in main investigation and follow-up [4] [6]
Response criterion in infancy — < 4 head turnings after sound

Follow up cf fig M 5	Main investigation protocol cf fig M:9								
N = 87 ♂ = 44 ♀ = 43	Smiles as response			Cooing			Silent when mother speaks		
Functions noted at examination:	φ	χ^2	signif.	φ	χ^2	signif.	φ	χ^2	signif.
Adequate smile in tester's opinion	.35	10.93	0.01	.56	6.95	0.01			
Speech developed							.51	44.37	0.01
Listens and answers to speech				.41	14.48	0.01	.34	9.87	0.05

instruction of the personnel handling the test. The psychological knowledge about the interest span of infants and the limited attention space before one year of age is important to the tester

BOEL calls for closeness and a you and-I relationship between the tester and the infant. Has this relationship been established, there is no difficulty in performing the test independently of acoustic milieu.

Trial preceding the construction [8] For the equipment of the first BOEL version the bell, attached to a silver ring and muffled to a lower intensity was preferred. A smaller mini-music box with lower intensity and higher frequency than that of the original one was added The visual stimulus was the short red stick The screening procedure was decided to be finished by a whisper from the rear

A WBC-nurse well aquainted with the main investigation was trained to assist. A well-baby clinic in a district under construction thus inhabited by many young families with small babies, was the main locality The mothers of infants ranging between the 5 months level to the 10 months level were asked, within the frame of the ordinary reception times, and without extra summonings if they were willing to participate.

The trial showed that the mini-music box, although still the most attractive sound source was disadvantageous because it had to be wound up which was easy to forget. The whisper was sometimes difficult to fulfill since the noise from the waiting room was too disturbing. The screening was usually found to be easy to fit into the daily program

Technical data and clinical calibration of sound sources [8] A trial series of 20 small silver sound sources formed more or less like bells and balls with different thickness and design were produced and subjected to technical-acoustical analysis.

Table D 3

Trial screening before the construction of BOEL.

Sex ♂	Sex ♀	Age in mths and days	Con-tact	Head-mov	Eye-cont.	Glance follows	Grasp.	Smile	Bell	Mini-music box	Whis-per	Voc.	Notes
	+	5.02	+	+	+	—	+	+	+	+	+	+	ref eye cl
+		5 10	+	+	+	+	—	+	+	+	+	+	
+		5 12	+	+	+	+	+	+	(+)	(+)	+	+	right s.
	+	5 19	+	+	+	+	+	+	(+)	+	+	—	right s.
	+	5.22	(+)	+	(+)	(+)	+	+	—	—	—	—	premat.
+		5_6	+	+	+	+	+	+	—	—	—	+	impat.
	+	5.28	+	+	+	+	+	+	—	—	+	—	noises
	+	5.29	+	+	+	+	+	+	+	+	+	+	
+		6.06	—	+	—	—	+	(+)	—	—	—	—	no it.
	+	6.08	+	+	+	(+)	+	+	+	+	+	+	interest
+		6.11	+	+	+	+	+	+	(+)	(+)	+	+	right s.
+		6.13	+	(+)	+	+	+	+	+	+	(+)	+	left s.
+		7.04	+	+	+	+	+	+	+	+	—	+	hurry
	+	7.20	+	+	+	+	+	+	+	+	+	+	interest
	+	8.00	+	+	+	+	+	+	+	+	+	+	interest
+		8.08	+	+	+	+	+	+	+	—	—	+	
+		8 17	—	—	—	—	—	—	—	—	—	—	screened ff
+		8_4	—	—	+	+	(+)	(+)	+	+	+	+	slow
	+	8.29	+	+	+	(+)	+	+	+	+	+	+	
	+	9.01	+	+	+	+	—	+	+	+	+	—	afraid
+		9.04	+	+	+	+	+	+	+	+	—	+	noises
+		9.07	+	+	+	+	+	+	+	+	+	+	fast resp.
	+	9.21	+	+	+	+	+	+	+	+	+	+	
+		10.09	+	+	+	+	+	+	+	+	+	+	
	+	10.10	+	+	+	+	+	+	+	+	+	+	birthw low
	+	10.18	+	+	+	+	+	+	+	+	+	+	

N = 26
13 ♂ 13 ♀

*) refers to doctor's reception hours

Then the types chosen were analyzed. The production included a control of weight and size both of the sound-board and the movable clapper

However the constructor was aware of the risk that informal sound sources like the silver bells involving manual sub-operations in the production course, could vary considerably with respect to acoustic components Even though the acoustic point of view as earlier stated, ought to be secondary as long as the organic hearing is not the main subject of the screening, the decision appeared motivated to check the technical data.

The acoustic analysis of the applied sound sources called for the assistance of the Department of Technical Audiology at the Karolinska Institutet, Stockholm.

A Hewlett-Packard Loudness Analyzer with 1/3 Octave bandpass filter built in and electronic memory was used. The spectral distribution of the sound energy at normal operation was analyzed, and

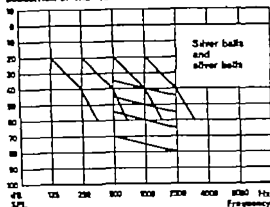


Fig D:3
The clinical calibration demonstrates the optimal area of audibility to hard-of-hearing children.

the sound pressure level was measured by means of a precision condensor microphone, Brüel & Kjaer type 4131 in free field, i.e the unechoic chamber of the Royal Institute of Technology

Two types of silver bells were chosen on the basis of the acoustic analysis obtained. One of them is called the ball since it is closed the other one is called the bell" since it is open. A second clinical calibration (cf fig D:3) was made, requesting the assistance of 72 hard-of hearing pupils at the Alvik School, 37 of them suffering from high-tone loss and 35 from flat loss

Half the 72 pupils had participated also in the earlier calibration. They were presented to the bell the ball" and two additional sound sources, the originally applied mini-music box and a brass bell, applied at the follow-up both to be found sonagraphed in fig M 8 Thus, 4 sound sources were presented, two of

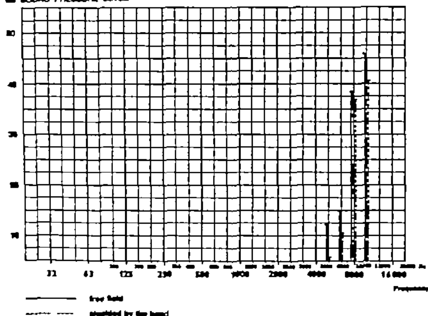


Fig D 4
Measurement of frequency and sound pressure range in silver bell in free field and shielded by the hand.

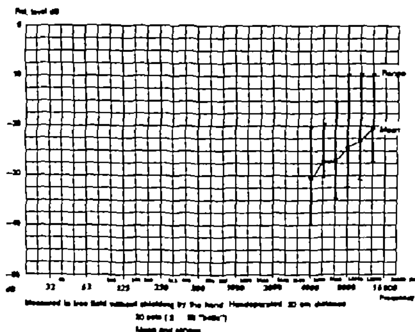


Fig. D:5
Measurement of 40 silver bells in BOEL equipments, selected by random sampling for check up regarding range of variation as to acoustic components [8].

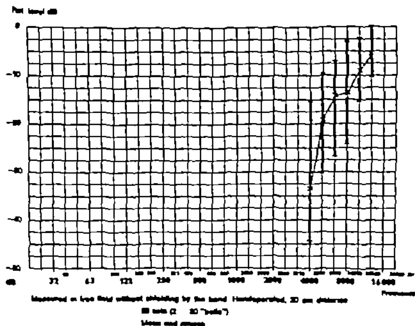


Fig. D-6
Measurement of 40 silver bells in BOEL equipments selected by random sampling for check up regarding range of variation as to acoustic components [8].

which were the real subjects for the calibration and the remaining two repre senting control sounds The presentation was rotated

This procedure on the calibration was caused by the experience of sound ex posures to be found among hard-of-hear ing pupils. Thus the pupils sometimes show an "over-ambition as to the per ception of sounds, since they are mature enough to be conscious of their handicap and eager to hide it. The brass bell and the mini-music box could be perceived by some of the pupils, (cf fig M 11 regard ing the mini-music box) The rotation was intended to prevent the risk of obtaining false negatives None of the children could hear any of the silver sound sources.

Thus, the construction of the *bell* and the *ball* was decided upon. The technical measurement of the bell is shown in fig D·4 both in free field and shielded with the hand viz the way it is operated at testing. The main frequencies are ranging between 4 000—12,500 Hz, and the sound pressure level does not exceed 45 dB measured at a distance of 20 cm from the sound source

In order to check the sound pressure variation caused by the partly manual production, the constructor decided upon the following control. Among the 100 sets of equipment designed for the Stockholm district, and already used for some months, 20 sets were selected by random sampling. In each set both sound types were represented by two sound sources. Figs D 5—6 show the means and ranges of sound pressure within the frequency band of 4 000 Hz to 12,500 Hz. None of the sound sources had components within the main speech sound area, and the mean of the sound pressure was 30—35 dB for the lowest frequency and 5—20 dB for the highest frequency It should be observed that the measurement is intended to allow no understatement of the eventual audibility to hard-of hearing children Thus, the mea surement was undertaken in free field, without shielding by the hand.

Practical data on the BOEL equipment [8]. BOEL is a name formed by the initial letters of the Swedish sentence Blicken Orienterar Efter Ljud meaning Look Orients After Sound The equipment is shown in figs D·7—12. In a steady box, designed to be neutral to the infant s attention, 4 silver sound sources and 2 visual stimuli are placed to be easily available although sheltered.

The main visual stimulus is the red gripper a double-sided wooden handle, designed to give a smooth feeling in the hand as well as in the infant s mouth The red color is intended to attract the infant s attention, and the length is meant to support the eye measure of the tester as it is exactly 20 cm which should be the approximate distance of the sound from the ear The gripper is prepared with boat varnish to endure much cleaning after use fig D·9

If the gripper for some reason, be unable to arouse interest or attention there is an additional visual stimulus available, intended to be used secondarily the silver mobile fig D 12 There are infants who appear sophisticated as to red toys perhaps because they have had much stimulance by red play toys at home. The gripper should always be tried

initially but when the infant persists in being uninterested the "mobile" should be tried. It consists of two concentric silver rings, being brought to whirl around the central stick to which they are attached. The use of the mobile calls for more care and handiness than the gripper. There is a risk that the hand movements may cause a sound from the inside of the palm, as a by-product"

The four small silver sound sources, representing frequencies above the main speech sound area, are meant to be fastened, two on each hand. To be easily movable, thus producing sounds without being caught sight of in the corner of the eye, they are attached by means of small loops at thin silver rings. The acoustic data are clear from figs D·4—6.

The balls are meant to be attached, one to each forefinger (fig D·8) and the bells one to each ring finger, all of them turned into the palm side of the hand, thus completely hidden when the fists are clenched. The ball is easily brought to sound by a slight movement with the forefinger (fig D 10) if necessary

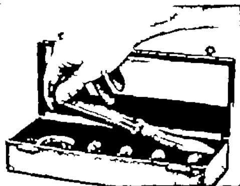


Fig D·7
The test equipment is placed in a steady box. A space is left for the forefinger to take the gripper easily without opening the clenched fist.

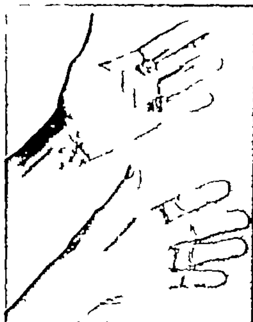


Fig D 8
The sound sources attached to the fingers, the balls to the forefingers, the bells to the ring fingers, turned into the palm side of the hand and practically invisible from the other side.

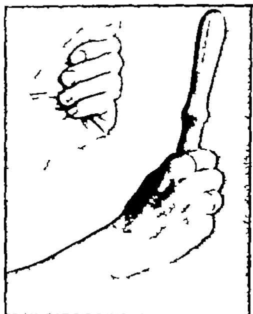


Fig D 9
The gripper is held like this with the fists clenched round the sound sources.



Fig D·10
A slight movement with the forefinger eventually combined with a little push of the thumb brings the ball to sound.

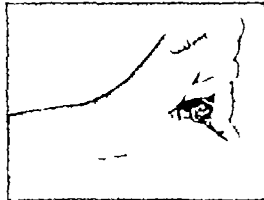


Fig D 11
An even slighter movement with the little finger is causing the bell to sound.

Photo Sven Didrik Bellander (D 7—D·12)

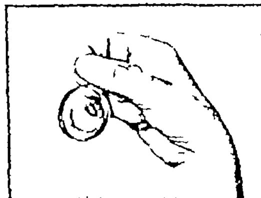


Fig D:1
The silver mobile calls for some handiness. It is very attractive to most infants, but the gripper should be used in the first place.

T sting procedure at BOEL screening [8]. At the initial establishing of a firm eye contact the infant should not be allowed to take the gripper It should be used to check the ability to follow a movement with the glance, first horizontally then vertically *figs* D·13—17 before the infant is taking it in order to put it into his mouth.



Fig D·13
Firm eye contact is est blished
Photo Wegne Lexau (D 13 D.37)



D.14
The eyes follow



D·15
first horizontally



D 16
then ertically upwards



D 17
and downwards



D 18
Then the infant is allowed to take the gripper



D 19
and put it into his mouth.



D 20



D 21
Cautiously the hidden sound source is brought up about 20 cm behind the infant ear while the tester tries to keep the contact. When the infant breaks the contact in order to search for the sound which has caught his attention, he has shown selective attention.



D 22
The visual contact is renewed, and new latent period should elapse



D 3
before the procedure is repeated to the other ear
The sound is presented



D 24
and the infant turns again.

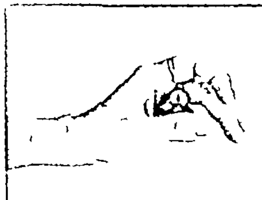


Fig D·10
A slight movement with the forefinger eventually combined with a little push of the thumb, brings the "ball" to sound.



Fig D·11
An even lighter movement with the little finger is causing the bell to sound.

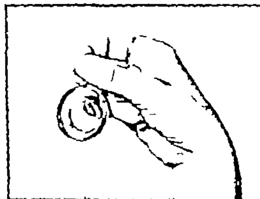


Photo Sten Didrik Bellander (D 7—D 12)

Fig D·12
The silver mobile calls for some handiness. It is very attractive to most infants, but the gripper should be used in the first place.

Testing procedure at BOEL screening [8]. At the initial establishing of a firm eye contact the infant should not be allowed to take the gripper. It should be used to check the ability to follow a movement with the glance, first horizontally then vertically figs D:13—17 before the infant is taking it in order to put it into his mouth.



Fig D·13
Firm eye contact is established
Photo Wanna Larsson (D 13—D 17)



D 14
The eyes follow



D·15
first horizontally

BOEL testing, it is important that she has sufficient knowledge also with regard to the social aspects of communicative disorders. However she is often accustomed to dealing with family problems regarding the development of infants as she is the one in our child medical care program who has the continuous contact through the first year of life

An orientation response should never be considered as a positive one if the preceding eye contact is uncertain or lacking The report from the test—which is carried through within a couple of minutes—is made on adhesive labels to be fastened at the WBC case sheet of the infant, fig D.28

Contact smile may be difficult to achieve in the actual test situation The WBC-nurse is allowed to fill in that square when she has known the infant long enough to have seen the smile in other connections and is convinced that the smile has an address The same is valid for vocalizations which the WBC nurse may have heard many times, but not in the test situation.

The WBC-nurse is instructed to make a retest when any of the squares has not been possible to fill in. If, after one or more retests within the upper age limit of <10 months any of the squares still has not been filled in, the WBC nurse is to keep the infant under observation in her future contact with him. Of course she informs and consults the available WBC pediatrician.

BOEL calls necessarily for the squares firm look eyes follow searches for ball and searches for bell to be filled in to be judged as positive.

Further the WBC-nurse is encouraged to talk to the parents if she feels that the infant could benefit by more environmental stimulation.

Evaluation problems [8]. Since January 1971 BOEL screening has been going on in Stockholm on a voluntary basis comprising 85 well-baby clinics The age limit of 7 months has been decided upon preliminarily regardless of sex. An upper limit of 9 months for a first testing, and 10 months for retesting, is applied.

The experience indicates that the 8 months limit may be the more suitable one even though the findings from the main investigation, regarding early developed and advanced infants, has turned out to be valid also on BOEL screening. The visual stimulus of the gripper appears—to this type of infants—to be unsatisfactory in some cases, although it is usually sufficient. The screening calls for swiftness and resolution in these cases as well.

The experience of Murphy[131] referred at p P 5 regarding the orienting response coming earlier to the right than to the left side has not been possible to confirm as yet. However the observations have been made on the BOEL testing that the infants in many cases do not turn to one of the sides, either right or left, until later at retesting. The eventual association with left handedness on turning to the left side could be an interesting scope for future research, possibly confirming Murphy's findings.

As BOEL, in the first place, is suggested to be a simple mass screening device and no formal psychological test the quanti-

Table D 2

The reliability of BOEL computed by test retest methodology [8]

N = 69 — Time interval ranging between 1 — 9 days.
♂ = 36
♀ = 33

BOEL I		BOEL II Negative	Positive	Total	φ	χ^2	Significance level
Motor stability							
includes "Steady back sits	—	35	4	39			
in mother's lap, potential	+	1	29	30			
ability to orient with distinct head-movements		36	33	69	.86	50 74	0.01
Eye contact							
includes Firm look	—	20	3	23			
before the gripper"	+	1	45	46	.87	52.06	0.01
is shown		1	48	69	.87	52.06	0.01
Attention visual/tactile							
includes Wants to take	—	30	4	34			
gripper" anticipation	+	0	35	35			
f Puts into mouth		30	39	69	.89	54 63	0.01
Attention visual							
includes Eyes follow"	—	[illegible]3	5	28			
visual stimulus horizon-	+	[illegible]	39	41			
tally and vertically		[illegible]5	44	69	79	42.99	0 01
Attention auditory							
includes "Searches for	—	25	4	29			
ball with distinct	+	1	39	40			
head-turning		26	43	69	.85	50.16	0.01
Attention aud tory							
includes Searches for	—	30	5	35			
bell with distinct	+	1	33	34			
head-turning		31	38	69	.83	47 76	0.01

fication for an interval scaling of different functions, fundamentally called for in most standardization procedures, has been estimated as superfluous. At the time of the experimental construction preceding the current equipment, neither the Bayley Scales of Infant Development[10] nor the Lindstam's Swedish standardization of Griffiths Mental Development Scale[110] were available

Later on, when the BOEL set up had been modified for the present outlook, the prospects of a conventional standardization to a higher degree became a topic of interest. The application in practice had pointed to the test giving more useful in-

formation regarding general infant development than originally was expected.

The classical test standardization, though, calls for the evaluation of both reliability and validity Since BOEL is applied during a period of infancy when the memory span is very short, the reliability could be comparatively easily achieved by using the test-retest method. As the development of faculties then still is rapid, it was favorable to make a short-term test-retest.

A limited test-retest series of 69 Stockholm infants is referred in table D.2. There are some squares of the label, with regard to the test retest method, which are preposterous as to correlations within the time span <14 days which should be a maximum intervall due to the rapid development changes in infancy No division into boys and girls has been made in this test-retest evaluation of BOEL s reliability

The traditional validity evaluation, though, requires a procedure by which each item should be subjected to the analysis of predictability as well as to an intercorrelationship As an empirical validity with this goal cannot be undertaken until a couple of years have elapsed so that the infants screened can be expected to have finished their first stage of speech development[80] a compromise was decided upon. The BOEL responses regarding searching for the presented sounds have been correlated with the outcome of Sheridan s Stycar Hearing Test[148] for 107 infants.

In short terms the Stycar test is performed like this, p 11[148]

— — — The examiner (E) should stand 1—3 feet to the side of the child (C) but outside his immediate range of vision. To ensure the most consistent results the sound stimulus should be given on a level with the ear — — —

The sounds are given at distances from 1½ feet (at 6 months) to 3 feet (9 months upwards) in the following order voice rattle spoon against cup tissue paper handbell The speech sounds are delivered at quiet conversational level They consist of the low frequency vowel OO repeated 2—4 times (e.g Oo-oo John Oo-oo) the high-pitched consonant sounds tit tit-tit, ps-ps-ps pth-pth-pth, repeated rapidly 3—6 times The remaining sounds are given for 1—2 seconds The rattle is shaken softly the tissue paper is rustled quietly the handbell is tinkled very gently and the spoon is merely stroked round the inside brim of the cup — — — If the first stimulus evokes no response E should wait for 2 seconds and then repeat it — — — "

The criterion for a positive response on the Stycar testing was decided to be head-turning in both directions after voice, rattle spoon, paper and bell, and for BOEL searches for ball and searches for bell with established firm look

The Stycar Hearing Test was performed by the investigator and an assistant. There are two correlations computed one between the first BOEL test called BOEL I below made by the WBC-nurse and the Stycar Hearing Test. The second correlation concerns the investigator's BOEL test, called BOEL II below and the Stycar Hearing Test. The practical course of events has been the following.

When the WBC-nurse has tested an infant without obtaining positive result,

one or more times, she has called for the investigator to come. The investigator has then, not only BOEL tested the infant, but also subjected him to the Stycar Hearing Test. Obtained correlations are shown in table D.3 below.

Table D·3

Correlations between BOEL attention screening test and the Stycar Hearing Test[11]

	BOEL I, tested by the WBC-nurse searches for both sounds			BOEL II tested by the investigator		
	— —	— +	Tot. N	— —	— +	Tot. N
STYCAR HEARING TEST	35	17	5	40	9	49
	+ —	+ +		+ —	+ +	
turns after 6 sounds	8	47	55	3	55	58
	43	64	107	43	64	107

The correlations are:			Sign. level
Stycar/Boel I	$\varphi = .538$	$\chi^2 = 57.55$	$p = 0.01$
Stycar/Boel II	$\varphi = .777$	$\chi^2 = 83.14$	$p = 0.01$

Positive associations found at the < 0.01 significance level show that in 76.6 % of testing cases BOEL is giving the same result as the Stycar even when presented by untrained staff. When presented by trained staff or at the upper age limit of the age span recommended for the BOEL testing, the correspondence is 88.8 %.

The adequate standardization of a scale of ability for infants is complicated, difficult, and time-consuming as recognized by Bayley[1]. Thus, the problem of a classical standardization was felt as a challenge for the next future. This was one of the main reasons why BOEL has been presented as a subject for discussion rather than a result. It is essential not to overinterpret the reliability and/or the validity before more experience is gathered from the practical application.

The methodological design of the BOEL screening may in the future call for a revision both of age limits and visual stimuli. The Stockholm trial is to be analyzed regarding these viewpoints. The aim is to survey the material of one year so that a basis for reference is obtained. This work has only started as yet.

The WBC nurse in the role of the modern family doctor. The inter action between the family and the WBC nurse in our country is unique provided that the nurse has met her situation with understanding, and that the family utilizes the facilities optimally. She meets the baby already the first week, often when he is only 5—6 days old.

Already at the maternity hospital the mother receives a brochure telling about the child health program offered by the community. The delivery department in-

forms the well-baby clinic of the district where the mother lives that the child was born. The mother is encouraged to contact the WBC as soon as she arrives home from the hospital

During the subsequent weeks and months regular contact is maintained regarding nourishment, care and general development, comprising check-ups of weight and growth, blood tests, vaccinations and so on. It is inevitable that the investigator involved in so many direct contacts with small infants and their mothers, considered the outstanding opportunities which are available both to the mothers and the child health organs of contributing to the puzzling bits of early communicative disorders and their detection.

Thus, the WBC nurses, having a good, allround medical training as well as experience of social family problems, are already used to telling parents about underdevelopment regarding the physical upbringing. It is possible that they are the best fitted category of the child health staff to inform about lacking contact with the environment as well, at least as a first step in the planning of a program for the infant.

In an undramatic way the WBC-nurses can advise the parents how to stimulate the infants in everyday situations. This does not mean that the specialist examination is superfluous. It only means that it is motivated that information should not be delayed, unless special conditions call for a postponement. Parents should have the right to be prepared in good time and to receive help with the planning of suitable stimulation for the infant.



Fig D 29
Elementary communicative traini g can be demonstrated to the mother by the WBC-nurse or an advisor f Lekotek [6a]
Photo Sara Dedrik Bellander

This calls for more exchange of information between the WBC and other institutions. The channels should be as open as possible between the more medically oriented birth delivery institutions, and the socially oriented child welfare programs. The continuity of care is basic

The need for an early screening of communicative preconditions is further stressed by the incidence of deviating development, including sight, hearing, and mental disturbances, found in the Gothenburg experiment with 4-years-of age check-ups of 796 children recently presented[10] based on a study from 1968

3 % of the 4 year-olds were reported to have impaired hearing and 7 % squinted and/or had sight reduction in one or both eyes. Only a small number of the sight defects had been discovered earlier. Even though severe congenital hearing defects were known earlier the necessity of detection already in infancy was emphasized.

The mental examinations resulted in the following conclusion. 17 percent, or



Fig D 30
The close "you-and-I"-relationship is basic to the stimulation of infants according to the BOEL program
Photo Kers Didrik Bellander

every sixth child aged *four* years, were found, on screening examination, to have an obvious or suspected mental retardation or/and a deviating behavior with respect to their chronological age indicating the need for a closer examination. — — — The deviations showed a significant association partly with perinatal conditions, and partly with a series of social factors. (p *1917*)

The results of this present study e.g. table R.2, show an interesting correspondence with the Gothenburg experience illustrated by the incidence of negative *responses to the attention test in infancy*. The key position of the visual attention and the check-up of eye contact in the method applied makes it probable that far more visual defects as an addition to the detection of imperfect sound attention, could be revealed if a screening of the BOEL type be a routine.

In their summary of the Gothenburg trial, Karlberg and von Sydow stress the possibility of preventing a lot of the discovered health deviations by some "rather simple measures to be taken within the frame of the child health program" (p 1918). Besides the early tracing activity repeated counseling is recommended regarding educational norms for infants and the need *for* emotional and developmental stimulance.

The resemblance with the BOEL program, which recommends the early cooperation with a "Lekotek"—an advisory bureau for training through play activity[159] on a home basis—is striking.

SUMMARY

Speech and language play such a central part in mental health that the prognosis for communicative development should be searched for within the child health program during the first year of life.

Communication, defined as the ex change of decoded signals, calls for the capacity to give priority to informative signals from the environment. The hypothesis is that normally the infant, in order to develop speech and language communication, has to show that he is able to pay selective attention, especially to sound signals

The reported study preceded by ex plorative methodological investigations [2] [3], comprises the examinations of 480 Stockholm infants 2½—13 months old [4] and the follow-up of 87 children aged 2½—3½ years [6] Its main aim has been

a) to study the attention pattern of infants to sound stimulation after visual at traction, and to establish its relation to age;

b) to find out if other factors than age influence the response behavior on testing attention in infancy·

c) to ascertain if an early test of sound attention in infancy predicts the future communicative behavior and speech

Earlier established methods have been tried, most of them developed with the starting point of hearing measurements With respect to the information aimed at —the infant s attention behavior—it was felt to be unnecessary to complicate an examination To be suitable for the child health program, a chosen testing technique should be mastered by one person, close at hand, because of the limited attention span of infants as well as of the unpredict able and variable acoustic milieu of most well-baby clinics

The capacity to shift attention focus may be tested by any sensori stimulation but it appeared reasonable to the investigator when dealing with infants less than one year of age, to start by catching the visual attention, as sight dominates the infant s attention field during the first three quarters period of life If the visual dominance remains when a sound atten tion test is performed, one can be certain that the infant really cares about the sound stimulus when leaving one attrac

tion to search for a second one, on principle less attractive

It is also easy to control the normal orientation response when attracting the visual attention as a first step The infant combines his visual attentiveness with the tactile one by stretching out his hands from approximately 5—6 months onwards.

An initial, firmly established eye contact was required before the presentation of sound stimuli. The sound sources preferred were constructed to be invisible to the infant. They were brought up 20—30 cm behind the infant's ear while the eye contact was held until they sounded, first at the one side then at the other Between the sound presentations the firm eye contact was re-established and the attention diverted by the visual stimulus

Among the visually attractive objects a short, red, round stick was found to be sufficiently stimulating. Nine sound presentations were tried, concluded by the voice and/or the whisper of the tester Adequate sound attention was considered to be present, if the infant oriented motorically and visually in the direction of the sound stimulus in spite of the attractive visual stimulus in front of his eyes. The criterion of a positive final result was 4 head-turnings after 5 sound presentations.

The suitability of the sound sources was estimated from three viewpoints. the percentage of positive responses in normal infants the inaudibility to hard-of hearing infants with residual hearing, and the practical possibility for one person alone to master the technique

The most suitable age level to screen attention behavior in the infant was found to be 7—9 months with an upper limit of 10 months for retest. Girls were found to respond at an average of about four weeks earlier than boys, and their response percentage was higher during the whole period of the first year of life The attention test was found to give information about other parts of the infant's development, e g. the capacity to watch and follow a movement, to reach for an attractive object and grasp it, and to orient with distinct head movements in the direction of the sound

The hypothesis—that infants who differ when exposed to sound stimuli will also differ regarding future speech development and communicative behavior—was confirmed two years later A strong positive association was shown between defective speech development and/or poor communication and negative response to the attention test in infancy

The discussion recommends the sex difference to be taken more into consideration when judging infant development, and suggests a correction-factor to be used for this purpose Further a communication nomogram suitable to child clinics is proposed as a desirable future program.

Finally the discussion presents the construction of the BOEL attention screening test based on the findings and applicable for infants 7—9 months old with the upper age limit of 10 months for retest. BOEL is a name formed by the initial letters of the Swedish sentence Blicken Orienterar Efter Ljud translated Look Orients After Sound

BOEL consists of 4 small silver sound

sources, designed to invisibly produce sound stimuli arousing interest in the infant, and 2 visual stimuli. The sounds should, furthermore not be perceptible to children with organic hearing impairment which can impede the spontaneous speech development. Therefore they are clinically calibrated by the assistance of 72 schoolchildren from the special classes for hard-of-hearing pupils

A tentative reliability and validity evaluation of the BOEL attention screening test is reported. BOEL is, since January 1971 subjected to a voluntary trial application in 85 well-baby clinics of the Stockholm area.

SAMMANFATTNING

Motiv för en interdisciplinär undersökning

Inom barnpsykiatrin och audiologin utgör de kontaktlösa barnen ett diagnostiskt och terapeutiskt problem. Bristande kontakt kan bero på hörsel och/eller synskador autism och andra psykiska störningar av olika slag, bristande miljöstimulans osv Allvarlig kontaktlöshet är ett hinder för både språklig utveckling och normalt kommunikativt beteende

Tal och språk intar en central plats i barns psykiska hälsa En viktig uppgift i samhällets barnhälsokontroll bör därför vara att redan tidigt skapa kännedom om barns förutsättningar för språklig inlärning. Några av de första bidragen till en prognos för talutvecklingsförloppet är ämnet för detta arbete.

Genom att tal och kommunikation är föremål för intresse inom foniatri, audiologi och pediatrik, pedagogik, psykologi och sociologi talöverföring och akustik samt fonetik och lingvistik har en tvärvetenskaplig arbetsinriktning varit nödvändig.

Kommunikationsbegreppets innebörd i utvecklingsförloppet hos barn

Kommunikation kan definieras som det fortlöpande utbytet av tolkade signaler mellan individ och omvärld. Signaler kan i sin tur kallas information. Tolkningen kräver centrala nervsystemets medverkan.

Förmåga att uppfatta, uttyda, diskriminera, integrera och till egna svarsmönster omforma de retningar som de utifrån kommande signalerna givit upphov till utgör grundvalen i uppbyggnaden av barnets språkliga funktioner vare sig dessa tar sig uttryck i aktiv talfärdighet och/eller passiv språkförståelse, eller när den första denotationsfasen övergår i den mognare fasen för manifest konnotation, som innebär en mer avancerad kognitiv utveckling.

Kommunikation kräver vidare organismens förmåga att sovra bland utifrån kommande signaler oavsett språkpsykologiska teorier om hur barn lär sig tala Tal förutsätter — för att bli kommunikativt — förmåga att träffa val.

Ljudets framträdande roll i det språkliga utbyte som är tal gör det rimligt att förmoda att barn tidigt måste börja välja vilka ljud de ska ägna uppmärksamhet, om de ska få del i omgivningens talkommunikation. Bland de ljudsignaler som fortlöpande överförs till hjärnan måste särskilt de lagras, som har relevans i den språkmiljö där barnet lever

Varje mänsklig färdighet kan förmodas få sitt optimum av utveckling om den inte blockeras "inom sin egen mognadsfas". Talfärdigheten ligger latent långt innan de första ordbildningarna börjar.

Dess förutsättningar bör klarläggas då — vilket betyder någon gång under tredje levnadskvartalet.

Hypotesen

Barns kommunikativa utveckling kräver en manifest selektiv uppmärksamhet. Bland utifrån kommande signaler måste i synnerhet ljudsignaler kunna prioriteras ifråga om uppmärksamhetsfokus.

Undersökningens uppläggning

a. *Förundersökningar* har utförts vid spädbarnshem och barnavårdscentraler för att en teknik skulle kunna renodlas, lämplig att använda inom barnhälsovården. Tidigare forskningsrön tillvaratogs härvid med avseende på stimuli och presentationssätt. Inriktningen var att finna en metod avsedd att kunna handhas av en person under de akustiska och övriga miljöförhållanden, som råder vid genomsnittet av stadens barnavårdscentraler.

b. En *representativundersökning* vidtog härefter, varvid den renodlade tekniken innebar att barnet efter inledande fast etablerad ögonkontakt och fokusering av den visuella uppmärksamheten bjöds en intresseväckande ljudretning utanför blickfältet. Ljudretningen skulle inte bara vara attraktiv för barnet. Ljudet skulle även akustiskt vara uppbyggt så att det inte till någon del av sin sammansättning återfanns inom det frekvensområde som kan uppfattas även av relativt gravt hörselskadade barn med hjälp av deras hörselrester.

Ljudets grundton borde återfinnas nå gonstans ovanför 4 000 Hz. Vidare borde ljudtrycksnivån vara lägre än vad som förekommer i talljudskomponenter vid så höga frekvenser. Därmed skulle man nå att icke blott barn med bristande intresse för ljud upptäcktes vid en testning, utan även de hörselskadade barn som inte kan tillägna sig tal spontant.

Representantivundersökningen syftade till att avgränsa den åldersnivå, vid vilken förutsättningarna är optimala att bedöma normaliteten i ett svarsmönster vid ljudretningar efter visuell avledning. Avsikten var att använda erfarenheterna för en utveckling av screening-metoder för barnhälsovården.

c. En *kalibrering* av de vid representativundersökningen använda ljudkällorna ansågs påkallad, för att ljudens eventuella hörbarhet för hörselskadade barn skulle kunna klarläggas på ett sätt som kunde utnyttjas för en fortsatt metodutveckling. Kalibreringen ansågs bäst fylla sitt syfte genom att ett antal hörselskadade skolbarn fick rapportera om de kunde uppfatta ljuden. S. k. "high tone loss" och "flat loss" var härvid representerade med genomsnittliga audiogram, som utvisade de "hörbarhetsområden" inom vilka ljuden befann sig.

d. *Intensivundersökning/follow-up* av ett stickprov bland representativundersökningens studieobjekt inriktades på att klarlägga, om samband föreligger mellan bristande svarsreaktion i spädbarnsåldern vid testning med den renodlade metod som tillämpats och senare kom-

munikativ utveckling, sådan denna tar sig uttryck i manifest talfärdighet och socialt beteende två år senare

Då testlitteraturen vid tidpunkten för intensivundersökningen inte omfattade svenska språkliga prov i tillfredsställande omfattning, sammanställdes ett material explorativt, avsett för 2½—3½ år gamla barn. Några uppgifter ur kända internationella utvecklingstester kombinerades med svenskspråkiga uppgifter Vidare sammanställdes ett enkelt foniatriskt schema för talstatus

Ursprungliga syftet var att utnyttja 4-årskontrollens resultat för en ytterligare uppföljning. På grund av den begränsade omfattning, i vilken denna kontroll företagits, kunde denna uppföljning ske endast för ett litet antal barn

Undersökningsmaterial

a *Förundersökningarna* omfattade dels 26 barn från Klingsta spädbarnshem i åldern 1—10 månader 13 pojkar och 13 flickor dels 134 spädbarn registrerade vid barnavårdscentraler i Stockholm i åldern 2—14 månader 68 pojkar och 66 flickor

b *Representativundersökningen* omfattade 480 spädbarn i åldern 2½—13 månader 265 pojkar och 215 flickor varav 460 var inskrivna vid barnavårdscentraler och 20 vid spädbarnshem.

c *Kalibreringen* skedde med assistans av 60 skolungdomar i åldern 7—17 år 26 med hörselnedsättning av typen high tone loss och 34 med flat loss sådan

d *Intensivundersökning/follow-up* efter 2 år och uppföljning genom 4-årskontrollen omfattade respektive 87 barn i åldern 2½—3½ år 44 pojkar och 43 flickor samt 51 barn 4—5 år 25 pojkar och 26 flickor

Resultat

Representativundersökningen gav vid handen följande resultat. Även om ljuduppmärksamhet finns redan kort efter födelsen, kan svarsbeteendet vid ett prov inte på ett diagnostiskt godtagbart sätt differentieras från annat sensomotoriskt svarsbeteende förrän ett spädbarn är omkring 7—8 månader om provet är avsett för screening. Tidigare blir procenten negativa svar på grund av psykomotorisk omognad så stor att screening inte "lönar sig Om ett ljud med intresseväckande "nyhetsvärde" når barnet i "närmiljö" orienterar barnet motoriskt och visuellt mot ljudsignalen även när det finns visuell stimulans framför ögonen. Den inledande ögonkontakten med barnet måste vara fast etablerad, innan ljudretning sker och kontakten måste återknytas före varje ny ljudretning. Orientering mot ljudkällan måste ske med distinkta huvudrörelser

Ljudkällor får inte avslöja sig genom sin storlek eller undersökarens handrörelser Eftersom visuell uppmärksamhet dominerar barns perceptionsfält intill 10-månadersåldern, befanns rimligt att som övre åldersgräns för ljuduppmärksamhetsprov föreslå 9 månader med en marginal för omtestning till 10-månadersstrecket. Finns visualdominansen kvar kan man vara säker på att det är fråga om äkta ljuduppmärksamhet, och att barnet verkligen bryr sig om ljudet när det orienterar efter det. Ljudets frekvens bör vara > 4 000 Hz, och ljudtrycket bör inte överskrida nivån 40—45 dB

Undersökningen visade vidare att en

klar könsskillnad förelåg ifråga om svarsberedskap vid uppmärksamhetsprov av den tillämpade typen. Flickor var ca en månad tidigare än pojkar och hade efter hela åldersskalan en högre svarsprocent, som utjämnades vid ettårsnivån, där dock barnantalet var för litet för slutsatser.

Förutom den funna könsskillnaden som tidigare forskare inte påvisat förrän under andra levnadsåret och/eller vid 18 månaders ålder framkom ett positivt samband på signifikansnivån 0.01 mellan flertalet deluppgifter i follow-up och resultatet av representativundersökningen. Uppföljningen med 4-årsundersökningen visade positiva korrelationer för resultat av tal och psykisk undersökning. Undersökningsmetoden fastslogs härigenom ha prediktionsvärde beträffande kommunikativt beteende efter 2 år. Korrelationerna med 4-årskontrollens resultat befanns tyda på enahanda förhållande, men undersökningsmaterialet ansågs för knapphändigt.

Som delresultat analyseras inflytandet på uppmärksamhetsprovets utfall av sådana omständigheter som yttre störningar ordningsnummer i syskonskara, komplikationer under grossess respektive förlossning, barnets "samarbetstyp" ifråga om allmän uppmärksamhet, psykomotorisk orienteringsförmåga, ögonkontakt och "intresse" samt ljudbildningsförmåga benämnd "artikulation".

En sådan störning som en polio-"spruta" före provet visade sig inte ha inflytande — barnets minnesspann är uppenbarligen alltför kort för att smärtan vid injektionen skall påverka senare uppmärksamhetsbeteende.

Signifikant högre negativ svarsprocent befanns föreligga för barn av senare ordningsföljd än "förstfödda" liksom för barn som saknar "artikulation" dvs. "tysta barn" med få ljudbildningar.

En ytterligare bekräftelse på könsskillnaden — väntad med hänsyn till tidigare undersökningar av fysisk utveckling hos flickor och pojkar — belyses genom den jämförelse av greppmotorikens utveckling som företogs på grund av det kända "samarbete" som råder mellan handmotorik och språkfunktion. Pojkarnas utveckling är även i detta avseende senare.

Diskussion

På grundval av resultaten förordas ett större hänsynstagande till könsskillnaden vid bedömning av spädbarns funktioner och färdigheter som skulle kunna uttryckas med en korrektionsfaktor. Det framhålles som önskvärt att man söker få fram ett kommunikations-nomogram användbart för kliniker.

Diskussionen framlägger vidare konstruktionen av uppmärksamhetsprovet BOEL. En tentativ reliabilitets- samt validitetsprövning* redovisas härvid. BOEL betyder Blicken Orienterar Efter Ljud och avser att screening-testa ljuduppmärksamheten hos barn 7—9 månader med en "respit" till 10 månader. Testet består av 4 små ljudkällor avsedda att producera ljudstimuli dolda för barnets blickar samt 2 visualstimuli. BOEL-testet är föremål för frivillig försöksverksamhet vid Stockholms barnavårdscentraler. Hittills tillämpas det, sedan januari 1971, vid 85 BVC.

*) Det engelska testet Sheridan Stycar Hearing Test har utgjort referens för validitetsprövning. Test-retestmetoden har använts för reliabilitets-beräkning.

Som diskussionsinlägg föreslås till sist BOEL-provet mer allmänt tillämpat inom barnhälsovården. Barnavårdscentralernas sjuksköterskor och därmed jämställda personalkategorier framhålles som lämpliga handhavare av screening-proven. Genom att det är lätt att administrera och efter instruktion och en kort undervisningskurs kan handhas av BVC-sköterskorna finns större möjligheter att tidigt upptäcka allvarliga kontaktstörningar än om metoden skulle kräva extra kallelser eller sådana personalkategorier som vårt samhälle har mera ont om t. ex. läkare eller psykologer Remitteringar till special klinik beräknas knappast bli föranledda i större utsträckning än nu är fallet. De kontaktstörda barnen blir inte fler genom BOEL-provet — de blir bara tidigare upptäckta.

Även om BOEL i första hand är avsett att sovra fram "uppmärksamhets-svaga" barn ger det samtidigt upplysningar om allmän utveckling, som kan tillvaratas, t. ex. huvudstabilitet, blickkontakt, ögonrörelser grip- och sittförmåga, kontakt leende och kommunikativa ljudbildningar

Representativundersökningen av spädbarn liksom efterundersökningen visar på tagliga överensstämmelser med det just framlagda Göteborgsförsöket med hälsokontroll av fyraåringar[99] Resultatet av ljuduppmärksamhetsprovet med den vid BOEL-screening tillämpade metoden (churu med 4 ljud som minimum i stället för 2) visade, tabell R.2, att genomsnitt ligen 20 % spädbarn i 7—9 månaders åldern icke svarat positivt, varvid den initiala blickkontakten hade en nyckelposition vid bedömningen.

Göteborgsförsöket redovisar hörselskador i fyraårsåldern med 3 % av försöksobjekten. Beträffande psykisk bedömning säges "17 proc. var sjätte fyraåring, be fanns vid screening-undersökning ha en klar till misstänkt utvecklinghämning eller /och ett icke ordinärt beteende för sin ålder och krävde närmare utredning. — — — Avvikelserna visade signifikant samband dels med perinatala förhållanden, dels med en rad sociala faktorer" (s. 1917)

Göteborgsförsöket påpekar vidare (s. 1918) att "en mycket stor del av dessa hälsoavvikelser är sådana som borde ha kunnat förebyggas genom tidigare vid tagna, delvis ganska enkla åtgärder inom barnhälsovårdens ram " och framhål ler i synnerhet syn- och hörselkontroll. "De svåra medfödda hörselfelen bör målmedvetet uppspåras av barnavårdscentralen redan under spädbarnsåret. — — — Dessutom bör man söka uppspåra sådana faktorer som kan tänkas förorsaka eller försvåra utvecklings- och beteende avvikelser så att man om möjligt kan minska deras skadeverkan."

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APPENDICES

APPENDIX I

Contents

Tabl A 1 T lutveckling och kommunikativ förmåga speech development and communicative ability

Teckenförklaring på svenska (Key to the signs in Swedish)

+ = föreligger (xists); Fp examination subject kön = sex, Ålder = age
– = föreligger j (does not exist); År mån + dgr = years months days

Meningsbildning (sentence formation)

L = långa meningar (long sentence) N = "normallängd (normal length)
K = korta meningar (short sentenc) I = inga meningsbildningar (no sentence formation)

Ordförråd (vocabulary)

S tort (large) N = "normalt (normal) L = litet (small) I = inget(none)

Prosodi (prosody)

N = "normal prosodi (normal prosody) P = perseveration (perseveration)

Funktione och fardigheter (functions and abiliti) jfr (f) (p) M 29 – M 30 (69–74) fig M 13–23

Ö = ögonkontakt (eye contact) BT = "bygga torn ("Tower") RT = "rundturen ("Color-Boat) BF byta f t vid gång i trappa ("Switch-back" change feet)
KB = "kulbrädet ("Pig-Board) NB = "Namna bilder" ("Name pictures)
F = form-plock-lådan ("Form-box) PT = pure tone generator ("PT")

Fonetisk realisation av fonem jf IPA[92] (Phoneti realisation of phoneme f signs used of IPA[92])

Fl frågor och anamne = th inve tigator questions and anamne i

Skratt (smile) M = mycket (much) N = "normalt (normal) F = "på f l ställ (in the wrong place)
A = allvarlig (serious)

Grepp, händhet (grasp handedness) F = fint utvecklad handmotorik (fine hand moter development) N = "normal handmotorik (normal hand motor devel opment) K = klumpig motorik (lumsy) V = vänsterhänthet (l fthandedness)
H = högerhänthet (righthandednes) + markering i båda rutorna betyd ingen preferens för höger ller vänster (+ mark means no preference for right left hand)

Graese partus (expectancy delivery); UA = utan anmärkning (nothing remarkabl) markering betyd komplikation (mark means complications)

Bedömning/spedbarnsund rsökningen (judgment/main investigation) OL = orientered fter 4 av 5 presenterade ljudretningar (head-turnings after 4 of 5 presented sound stimuli) ER = "rod ryttare öve var för ung vid spedbarnsudd redsökningen ller orienterade fter farre ka 4 ljudretningar på ad kvat sätt (too young t the main investigation or turned hi head after l ss than 4 sound stimuli in an adequate way) A vvike (deviating behavior)

Bedömning/efterund rsökningen (judgment/f llow-up) N = "normal språklig utveckling (normal language development) K kommunikation med omvärlden (communication with the environment) U = uttal (pronunciation) TU tal utveckling (speech development)

Tabl A 2

Teckenforklaring på svenska återfinns över tabellhuvudet (Key to the igns in Swedish to be find above the tabl)

The phoneti transcription has been made by rdinary typing The brackets have been xeluded because of limited space The f llowing abbreviations mean

E-u = f llow-up two years afte the main investigation; Bedomn = judgment

Sp-u. = the main investigation; Kon = sex; Ålder i år mån + dgr = age tc

Vok = all vowel phoneme except / /

s-komb = combinations with /s/ and one or more consonants i lusters initial intermediant final

Benamn under rubriken Fargidentifikat etc = the fi st column refers to the ability to name lor the second one to identificat on through association

Othe abbrevi tions in the tabl mean

sub = substitutions ibl = sometime existent u = adequate k = ithe f the consonants in the luste is pronunced omk. = metathesi ph*

sakn = missing phoneme or ombinations f phoneme nasal = nasalization

dift = diphtongization dial = dialectal pronunciation metat = meta-

the is** l; -insk = xtra sounds reduplications etc dist = di tortions irregular

Semantik = semanti i semanti ability comprehension

Brackets around data-varying occurence sometime adequately occuring

*) metathe regarding phoneme i transposition of phoneme

**) transposition of phoneme sequence etc

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A P P E N D I X   II

Contents

Tableau in Swedish with comments showing the meaning category and acceptable names for identified pictures on item "Name pictures" of the follow-up regarding verbal ability in 87 Stockholm children examined two years after the main investigation of sound attention in infancy

APPENDIX II

cf p H 28

Tablå över innebörd, kategori och benämning av bilder i uppgift nr 6 vid återundersökning av talutveckling och kommunikativ förmåga ho 87 stockholmsbarn, undersökta i spädbarnsålder ra med varande på sel k tiv ljuduppmärksamhet (4) (8) Uppgift nr 6 = "Nämna bilder"

Nämna bilder" var ett renodlat verbalt prov som fordrad att barnet fte uppmaning skull tala om vad tolv bilder f reställd som framgår av fig H 18 och H 19 H:28 (72) För vede börande åldersnivå måste tt sådant prov innebära tt alternativa benämningar godkändes unde förutsättning att rimliga krav på adekvat semantik tillgodosågs Tablån upptar godkända benämningar i ordningsföljd efte svarsordet frekvens Allofone v /ɔ/ i t ex. "kopp vovve boll v /a/ t x. /ɑ/ (läspljud) och av /a/ i t ex. "mugg hund samt närvaro respektive frånvaro av supradentalen i t ex. "björn antecknade på protokollet for talstatus Jfr pkt 6 på H 28 (72)

Bild föreställande (Pi ture meaning) (Cf p H 28 /72/)	Adekvat kategori: (Adequate category:)	Godkända alternat benämn (Ac epted alternative name)
Fli ka med gult hår flät rod klänning vitt förkläde	Barn flicka, docka	Docka flicka pojke barn klänning
Gul mugg med rod saft	Rod dryck i drickredskap t x. kopp	Kopp saft mugg choklad
Rod pall	Sittmöbel utan ryggstod	Stol pall bänk
Rod hink med sand i gul sandspade	Y rktyg for sandlek	Sand spade leka sanden sked
Rod leksaksbil med ing-lande andr	Fordon, personbil	Bil orm (sobret mi stelkades)
Rott lokomotiv	Leksaksl k	Tåg lastbil bil hus
Rod lastbil med gult flak och range last	Fordon lastbil	Bil lastbil traktor
Prästkrage	Blomma	Blomma
Boll i färgerna rott gult blått och grått	Boll	Boll kula ballong
Leksaksanka på stiliserad vågor	Fågel i leksaksdjur	Anka and pippi svan fågel höna
Teddybjörn, orangefärgad	Leksaksdjur	Nalle björn hund

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MICROANGIOGRAPHY OF THE LIVER

AN EXPERIMENTAL STUDY OF SHEEP FROM THE PRENATAL TO THE FULLGROWN PERIOD

BY HEIKKI WENDELIN

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM SWEDEN

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MICROANGIOGRAPHY OF THE LIVER

An experimental study of sheep from the prenatal to the fullgrown period

TO THE EWES

ACTA PAEDIATRICA SCANDINAVICA

SUPPLEMENT 233, 19

From the Cardiorespiratory Research Unit (Head Professor Tuomas Peltonen, M.D.)
and the Department of Pathology (Head Professor Osmo Järvi, M.D.)
University of Turku, Turku, Finland

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An experimental study of sheep from the prenatal to the fullgrown period

BY

HEIKKI WENDELIN

TURKU 1972

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CONTENTS

INTRODUCTION AND AIM OF STUDY

The literature dealing with the hepatic circulation has since Galen's days (99) reached such proportions that a thorough look into it makes a modern reader feel at times overwhelmed. At the same time this vast literature is proof both of how vitally important the hepatic circulation is for the functioning of the vertebrates' organism and of the abundance of methods of study and the difficulties in applying them. Contradictions in the results of the various methods are in ample supply.

At the beginning of this century Mall (75) gave quite a detailed account of the hepatic vascular pattern and stated that the adult afferent and efferent vascular pattern has, in the human fetus, been shaped as early as in the eighth fetal week. This observation has been supported by subsequent authors. There are two reasons why significant differences between the pre- and the postnatal period in the vascular pattern of the liver could be expected. 1) In the fetal period the liver is the largest hemopoietic organ, whereas it in the adult is of fundamental importance for the metabolism of the organism. 2) In the fetal period the liver receives its blood mainly from the umbilical vein, a great part of the blood thus supplied being conducted through the ductus venosus directly to the inferior caval vein as Barclay and co-workers (8) and after him many other authors have proved by means of cineangiography. As the umbilical circulation is cut off at birth the liver receives blood from the portal vein and from the hepatic artery. When the ductus venosus has closed, all of the blood from the portal vein flows through the capillaries into the hepatic veins.

The present, generally accepted opinion of the microscopic morphology of the mammal's liver is based on the work of Elias (32, 33) in which is shown that the liver is a continuous mass of parenchymatous cells tunnelled by special capillaries called sinusoids. The capillary level's relationship to the parenchymatous cells and its joining the afferent and the efferent vascular pattern have been studied by numerous, both static and dynamic methods. The reliability of many findings has thus been confirmed, but often the results obtained have differed from each other.

In connection with the studies of the fetal and the neonatal circulation the morphology of the macroscopic blood vessels of the liver has been clarified to a great extent (59, 60, 8). It was found to be sensible to direct the examinations also to the capillary level of the liver, of which our knowledge, especially regarding the fetal period, is based on rather few studies.

Among the methods of studying the microvascular pattern microangiography has gained a secure foothold primarily due to Barclay (6) and Bellman (11) who have comprehensively dealt with the basis and details of the method. This method has also been adapted to the study of the hepatic circulation and concerning the adult the results have often tallied as compared to those obtained with other methods and have to some extent, also supplemented the earlier picture of the liver. On the other hand, microangiographical ex

aminations of the liver in the fetal period have not been made.

The *aim of this study* is, by the use of microangiography to give an account of the vascular pattern of the liver in the fetal, neonatal and adult period and compare these to each other both qualitatively and quantitatively and to supplement the picture of the microvascular pattern of the liver in the mammal by using the sheep as test animal

METHODS IN STUDIES OF THE MICROARCHITECTURE OF THE HEPATIC CIRCULATION

The methods of studying the hepatic microcirculation can be divided either into dynamic or static methods according to whether the examination is made in vivo or in vitro

Morphological studies *in vivo* have [illegible] been made by observing the transilluminated liver's edge under a microscope (16 64 77 78, 85 92, 98, 107) By injecting a radiopaque contrast medium into the vessels leading to the liver an attempt has, by means of the cineangiographic technique been made to radiograph the microcirculation (76, 90) With the aid of physiological data, obtained by perfusion examinations of the liver it has been endeavoured to clarify the anatomical relations (2, 45 4[illegible])

Studies of the microangiology of the liver made under *in vitro* conditions are numerous. The earliest studies were made by histological methods (19 63) The picture of the microanatomy of the liver constructed with the aid of serial sections, is to a great extent based on the study made by Elias (32, 33) The histological picture has often been supplemented by injecting a stain into the blood vessels before preparing the sections (4, 33 75 82, 86 91) In addition to using a conventional light microscope in the studies of the hepatic circulation the electron microscope has also been employed (70 104) By infusing the hepatic blood vessels for a cast the anatomy of the small vessels has been studied since the beginning of this century (29 54 68, 73, 73 76 79 107) After radiography of the microscopic sections had become possible (50) this method has been adapted to the examination of small blood vessels infused with a radiopaque contrast medium. In addition to sporadic microangiographic radiographs of the liver (17 106) primarily centred upon this method, studies have later been presented, in which microangiography of the liver has been more thoroughly dealt with (13, 14, 21 25 93)

EMBRYOLOGY OF THE HEPATIC CIRCULATION

Early development of the hepatic tissue

The primordium of the liver is developed from the endoderm of the foregut (67 70 71, 101) and in man and several other mammals also from the coelomic mesoderm (34) (Fig 1) All authors are not completely convinced of the reliability of the mesodermal origin (31) When the human fetus is 4 mm in size the proliferous cells of the endodermal liver diverticulum and of the mesoderm of the coelom penetrate into the ventral mesentery and the septum transversum, of the mesenchyme of which the supporting tissue of the developing liver is formed and in which the primordial sinusoids are located. As the omphalomesenteric veins join the developing sinusoids the capillary network is formed, which is lined with the epithelial cell tissue of the liver primordium. In the fetal period

the cells are in several layers around the capillaries, but begin, in most mammals, after birth to arrange themselves into a one cell thick system of liver plates, the muralium, inside of which is the sinusoidal network spreading throughout the liver parenchyma. According to Morgan and Hartroft (84) the liver plates in man are not one cell thick all through the liver until in the fifth year of age.

Development of the venous system

Of the blood islands developing in the splanchnic mesoderm of the yolk sac is formed the omphalomesenteric venous plexus, which in man can be observed when the fetus is 2.5—4.3 mm long (101) (Fig. 1) As the venous plexus grows two larger blood vessels are developed, the right and the left omphalomesenteric vein which drain into the sinus venosus of the heart together with the paired umbilical and cardinal veins. In a 4 mm fetus the omphalomesenteric veins from both sides of the liver drain into the developing liver parenchyma and join the primordial sinusoidal network, which hence forth acts as junction for the proximal and distal parts of the omphalomesenteric veins (30 89) When the fetus measures 5 mm four larger anastomoses are formed between the omphalomesenteric veins (30) Of these anastomoses one is located under the diaphragm between the proximal parts of the veins (not seen in Fig 1) and the others under the liver between the distal parts of the veins in such a way that the first is on the ventral side of the duodenum, the next on the dorsal side and the last under the duodenum. In an 8 mm fetus the final hepatic venous and portal venous system begins to take form, and at the 9 mm stage it is fully developed as regards its main characteristics.

Hepatic veins From the proximal part of the right omphalomesenteric vein and the right half of the anastomosis under the diaphragm are developed the right hepatic vein and the common hepatic vein. The proximal part of the left omphalomesenteric vein atrophies as far as to the anastomosis on the dorsal side of the duodenum, and the left half of the anastomosis located under the diaphragm joins several new small branches and forms the left hepatic veins. In a 9 mm fetus the common hepatic vein can be regarded as the inferior caval vein into which the hepatic veins drain (23 30)

Portal vein The distal part of the right omphalomesenteric vein atrophies caudally from the dorsal anastomosis and the left one cranially from here. After the most caudal anastomosis has atrophied the remaining distal parts of the omphalomesenteric veins, together with the dorsal anastomosis, form an S-shaped vein, which becomes the portal vein. The superior mesenteric vein and the splenic veins formed in situ join the left omphalomesenteric vein, which is located caudally from the dorsal anastomosis and which forms the starting point of the portal vein (23 30)

Umbilical veins When the fetus measures 5 mm both umbilical veins anastomose with the venous plexus of the liver whereat the left one first loses its communication with the sinus venosus and the right umbilical vein then is completely obliterated.

As the umbilical blood circulation changes its course from extrahepatic to intrahepatic, within the liver of most mammals the *ductus venosus* is developed, which in a 5 mm human fetus forms a shunt between the subdiaphragmatic and the cranial subhepatic anastomosis (30) With the aid of this the blood of the left umbilical vein in a 7.5 mm fetus is conducted to the common hepatic vein. Later the non-branching ductus venosus connects the umbilical vein directly with the inferior caval vein, into which it drains together with the veins from the left lobe of the liver (8 30 69 83) The right half of the subhepatic anastomosis connects the portal circulation with the intrahepatic branches of the left umbilical vein. This connection forms the sinus intermedius in a 9 mm fetus (8 30)

Development of the arteries

The hepatic arteries probably originate from the arteries supplying the septum transversum (89) but at which stage they join the sinusoids is not known The capillary network formed by the omphalomesenteric veins and the primordial sinusoids may together with the arteries in the septum transversum, form arterio-venous anastomoses, which could explain why the arteries later drain directly into the sinusoids (22)

Development of the sinusoidal network

In the septum transversum the primordial capillary network is formed by separate endothelial vesicles and branches of the omphalomesenteric veins joining these into which network's mesenchyme of loops the cells developing into the liver penetrate when the fetus measures 3—4 mm (34 71) According to Streeter (101) a large part of the primitive sinusoidal network is developed from the blood islands formed in situ, the omphalomesenteric veins connected to these also changing into sinusoids. The angiogenetic stimulus in this region is evidently produced by the interaction between the capillary network and the developing hepatic cell tissue (100 101) With the development of the sinusoidal network the afferent portal venules and the efferent central veins characteristic of the adult liver are soon formed.

FETAL AND NEONATAL HEPATIC CIRCULATION

Macroscopic structure

The general structure of the hepatic vascular pattern already resembles the adult one at a very early stage of the development of the fetus, as Mall (75) has shown. The hepatic artery and the portal vein are arranged segmentally the hepatic veins intersegmentally as in the adult (56) The characteristic feature of the fetal circulation is the ductus venosus, which conducts part of the umbilical blood directly into the inferior caval vein. Before the ductus venosus numerous branches from the umbilical vein enter the liver into its left half, which in the fetal period is relatively large After the ductus venosus the umbilical vein, the sinus intermedia acting as intermediary joins the portal circulation through which the right half of the liver receives most of its blood (8 69 8) Although the ductus venosus for a long time has been known as the characteristic feature of the fetal circulation (Vesalius 1543, ref. 83) its significance is still unclear In most mammals it is open until birth, in the horse and the pig it closes at the early stage of pregnancy

In the distal end of the non-branching ductus venosus is a "sphincter" nerved by the vagus nerve (10) or by the sympathicus (8) or by both of these (5 87) which regulates the flow of blood through the ductus venosus and the sinusoids of the liver

During the fetal period the flow in the *narrowly luminal hepatic arteries is, on the* basis of X ray examinations with contrast media, negligible compared to the portal and the umbilical circulations (8 69 87)

As the fetus connection with the mother by means of the umbilical cord, is cut off at the moment of birth, the liver receives its blood mainly from the portal vein and partly from the hepatic artery

Microscopic structure

Venous system The vascular patterns of both the portal and the hepatic veins in a new born human being resemble a short and stunted tree (83)

The portal vein very soon branches out into short separate vascular segments of diminishing calibre, due to which the portal vasculature by nature is more terminal than in

the adult, in whom the branches of the portal vein gradually are divided into secondary and further into terminal branches. The preterminal branches observed in adults are rarely found.

Also the hepatic venous system seems short and stunted in the new-born and the sinusoids drain into the hepatic vein almost along its full length as far as to the larger branches with the exception of the main branches, which are separated from the parenchyma by Glisson's capsule. The finely divided branching into central and sublobular hepatic veins, characteristic of the adult, is missing in the new-born (83). In the rabbit fetus it has been possible to make out both central and sublobular hepatic veins. The distal segments of these as well as of the portal venules are short and stunted and closer to each other than in the fullgrown rabbit with the consequence that the translobular distance of the portal and the central venules is shorter than in the adult (78).

Hepatic artery. In the new-born human being it has been found that the hepatic artery in comparison to the corresponding branch of the portal vein is larger than in the adult, which has been regarded as a result of the inactivity of the portal blood flow during the fetal period (83). According to Tajiri (103) the main part of the terminal arteria capillaries in a 3—4 month old human fetus drains into the interlobular hemopoietic tissue and from here further into the sinusoids. Later when the hemopoietic tissue has atrophied, the arteria capillaries join the sinusoids directly. In the rabbit fetus has rarely been found any open hepatic arterioles and only close to birth (78). These drain into the sinusoids as in the adult, either directly through the arterio-sinus twig or through the functional arterio-portal anastomosis, whereat the blood from the arterio-sinus twig is led into the portal venules and from here further into the sinusoids. The reversal of the portal blood flow observed in the adult has not been found when the arterio-portal anastomosis dilates and the blood is led into the portal venules.

Sinusoidal network. The sinusoids are according to Montagnani (83) in the new-born human being arranged radially around the portal triads forming the so-called portal lobule (19, 75, 91), which is the opposite of the hepatic lobule suggested by Kiernan (63), in which the sinusoidal network extends radially towards the central vein. It is not a question of an anatomical fact but of an impression due to the pressure conditions prevailing in the hepatic vein and the portal vein, an impression which it has been possible to verify by tests (40). When the pressure in the hepatic vein exceeds that of the portal vein, as it does in the fetus, the sinusoids in a liver section seem to settle around the portal veins. In the adult again the portal pressure is higher than the pressure in the hepatic vein, whereat the sinusoids seem to have settled around the central vein. The calibre of the sinusoids is either the same as in the adult (83) or slightly greater (78). Compared to the cylinder like sinusoids proceeding in a straight line in the adult, the sinusoids in the rabbit fetus have been found to be lumenwise irregular and arranged tortuously resembling a "honeycomb cell" (78). No significant differences between the microcirculation in the left and the right half of the liver have been found in the rabbit fetus (78).

MICROSCOPIC STRUCTURE OF THE ADULT HEPATIC CIRCULATION

Most of the papers dealing with the liver are agreed on the main characteristics of the adult internal hepatic microvascularization and on its similarity in most mammals and also in some lower vertebrates (1, 18, 22, 35, 39, 75, 89) (Fig. 2). There are, however, details, in which the results obtained by different authors and different methods of study have partly differed from each other.

Portal vein

After penetrating the porta hepatis the portal vein branches out segmentally into several branches throughout the liver substance. According to many authors the large portal branches do not directly vascularize the surrounding parenchyma (45 79 89 107) According to Elias (33) smaller veins, marginal distributing veins, proceed to the portal canal from the larger conducting veins. These marginal distributing veins run parallel to the larger veins and drain into the sinusoids through the inlet venules. Contrary to what is the case in man and in the dog, marginal distributing veins are rare in the rat, due to which the surroundings of the large portal veins are poorly vascularized (21, 46) leading, in an experimental dietary cirrhosis, to the appearance of fibrosis in the rat, mostly in the proximity of the large portal canals (53) In the rabbit has been found a direct draining into the sinusoids also from the large portal veins through the vein penetrating into the interlobular space (93) In the study by Lozano and Andrews (73) has been suggested that in many mammals branches the size of inlet venules proceed from portal branches of all sizes, although they are rare in the largest portal veins. In these studies, in which there from the large portal veins is direct draining into the sinusoids, the small branches acting as intermediaries, it has not been possible to show any marginal distributing veins.

The terminal branches of the portal vein penetrate into the interlobular spaces, in which one vein (the axial distributing vein, ref. 33) lets blood into the sinusoids of more than one lobule through the inlet venules. The inlet venules perforate the so-called limiting plate lining the portal canals as does the terminal end (or twig) of the portal venules, which is immediately divided into the sinusoids (33)

Communications, passing the sinusoids, between the portal vein and the hepatic vein have been found in man (24, 55) and in some other mammals (73 92) although these observations have generally been rare Likewise anastomoses between the different portal veins are rare and according to Elias and Sherrick (39) they do not normally occur in vessels larger than those at the terminal end level.

Hepatic artery

The branches of the hepatic artery penetrate through the porta hepatis, into the liver and follow closely the branches of the portal vein The cross section of the hepatic artery is ¼ of the portal vein (18) and it has been found that one portal vein, in the same portal canal is accompanied by two or several, with one another anastomosing hepatic arteries (37 108) Until the precapillary level the arteries of the different territories of the liver are with one another non-anastomosing end arteries (49) but the terminal and subcapsular branches have been found to anastomose with one another (80 103)

There are several studies of the terminal distribution of the hepatic artery in which attention has been paid to its termination 1) in the wall of the bile ducts forming the periductal plexus, which joins the sinusoids and the portal system by means of small vessels, 2) directly in the sinusoids, 3) in the walls of the blood vessels as vasa vasorum and 4) directly in the hepatic vein or the portal vein to form an arterio-venous anastomosis

Elias and Petty (37) have suggested that the only arterio-portal anastomosis is the periductal plexus. Neither have many others found any direct arterio-portal anastomoses (21, 54 76 86 93) In most vital-microscopic examinations has been shown that the terminal branches of the hepatic artery anastomose with the portal vein in many animal species (15 64 98, 107) This anastomosis has also been seen in examinations by means of injections in man and in some other mammals (23 47 68, 73 82) According to some studies the anastomoses are not structural but functional as the thin arterial branch drains right

into the beginning of the sinusoid (77 85) The observations of the anastomoses between the hepatic artery and the hepatic vein (2, 3, 107) and between the periductal plexus and the hepatic vein (73) are rare and in most studies it has not been possible to find them.

Wakim and Mann (107) Elias (33) and Tajiri (103) have found that the arteria capillaries drain into both the peripheral and the central sinusoids of the hepatic lobule. In subsequent studies these intralobular arteries have not been found but the arterioles have drained only into the peripheral sinuses (54 73, 82, 93) Many authors find that the arterial blood flow directly to the sinusoids is minimal compared to the flow coming indirectly through the periductal plexus and the arterio-venous anastomoses (64, 74, 82, 93) It has been noted that the hepatic capsule receives arterial blood also from the phrenic arteries *and the branches coming from the internal* mammary arteries, which anastomose with the subcapsular terminal hepatic arterioles (80, 103)

Hepatic vein

The hepatic venous system begins with the central veins, which drain into the sublobular veins and these further into the collecting veins. From the liver the blood escapes into the inferior caval vein. The hepatic veins are firmly imbricated with the portal veins, but are not arranged segmentally only unite the liver to one continuous vascular pattern. In some studies has been found that the branches of the hepatic veins in man anastomose with one another (24 37 76)

Since the sinusoids in man drain solely into the central veins the regions around the sublobular and the larger hepatic veins are poorly vascularized (35) In the rat (46, 54) separate sinusoids can drain into any level of the hepatic venous system and in this respect there are no poorly vascularized regions.

Around the hepatic veins are spiral muscles and sphincters, which in the dog may when contracting stop the flow altogether (35, 105) but which in man are relatively insignificant (48)

Sinusoidal network

According to the opinion formed by Elias (32) the parenchyma of the liver is a muralium, of which the walls in the mammals are one cell thick and in lower vertebrates mainly two cells thick. The spaces left between the parenchymatous cells, the lacunae hepatis, form a labyrinth continuing throughout, in which the hepatic sinusoids are located. The blood from the portal space drains into the sinusoids, which in turn drain into the central vein or possibly also into the sublobular hepatic venule through the so-called sluice channels (28 74) *and in the rat along* all the length of the hepatic vein (38, 54) In both the portal and the hepatic end of the sinusoids is a sphincter (15 64 77) which electron microscopically is an endothelial or reticuloendothelial cell (20) Also within the sinusoids the walls are lined with corresponding cells, which are actively phagocytic (64) The perisinusoidal space (Disse) remaining between the cells lining the sinusoids and the hepatic parenchymatous cells, which is filled with plasma, is clearly seen under a light microscope in postmortem sections, apparently due to anoxia (88) but equally clearly under an electron microscope in specimens taken in vivo (104)

The classical concept of the hepatic lobule, which was first presented by Kiernan (63) is actually only to be found in the adult pig polar bear and camel, in which the septa divide the liver into lobules (36) These septa of connective tissue are not found in man nor in most other mammals. The sinusoids converging from the portal region to the central vein give, in a liver section, the impression of the hexagonal area called the hepatic lobule. This picture, however depends on the intra-

hepatic blood pressure conditions because if the pressure of the hepatic vein changes to become greater than that of the portal vein, a picture is formed, in which the sinusoids are turned towards the portal vein, the portal lobule (9 40)

Rappaport *et al* (91) have suggested as a basal both structural and functional concept of hepatic unit the hepatic acinus, which is "an irregular microscopic clump of tissue arranged around a trio of terminal branches of the hepatic artery portal vein and the bile duct branching out from the smallest triangular portal space and *interdigitating with* the terminal hepatic veins The hepatic acinus consists of the parallel sectors of two hexagonal hepatic lobules next to each other reaching from the central vein of one to the other The region of the acinus nearest to the triad is vascularized with fresh blood and the further away from the central vein one proceeds the less nutrients there are in the blood.

MATERIAL AND METHODS

The whol material comprised 39 Finn sheep which represented both sexes. In Table 1 is seen the number of test animals in the different age groups and under the different test conditions. All the fetuses were delivered by a cesarean section close to the estimated time of spontaneous birth. The age of those spontaneously born ranged from ½—6 days. The young sheep were 2—4 months old and the fullgrown 1—1½ years old.

The microangiographic technique applied in this study is mainly based on the results obtained in the study comparing different methods by Wendelin and Lindgren (109).

The animals were anesthetized with pentobarbitone sodium (Nembutal® Abbot) and heparinized (dose of 5000—25000 I.U.). For the injection the blood vessels leading to the liver were cannulated with polyethyline tubes in a laparotomy. As contrast medium was mainly used Chromopaque® (Damancy & Co. Ltd.) which had been diluted with physiologic saline to 10 %. On 9 fetuses and 5 spontaneously born the injection was made using a barium sulfate suspension (Micropaque® Damancy & Co. Ltd.) diluted in the same way. The infusion was done with a constant, by a Hg manometer controlled pressure corresponding to the physiological pressure conditions in the blood vessel at +37 C. The infusion suspension was by means of a thermoregulated magnetic stirrer kept homogeneous throughout the

Table 1. *The number of animals in different age and injection groups*

Age	Weight (kg)	Site of injection (No. of animals)				Total number of animals in different age groups
		portal vein	hepatic artery	hepatic vein	portal vein and hepatic artery	
Fetal	..4 (1.0—3.1)	5	4	2		13
½—6 days	3.8 (..3—6.0)	4	10		1	17
2—4 months	13.0 (8.8—19.0)	1	2	1	1	5
1—1½ years	5.0 (25.0—30.0)	1	1	1	1	4
Total		11	17	6	5	39

injection, which lasted for an hour on the average The test animal died just before or during the injection.

The injection into the portal vein was on the new-born lambs made through the umbilical vein and on the young and fullgrown sheep directly into the portal vein. The inferior caval vein was immediately opened above the diaphragm and the hepatic arteries in the region of the hepatic hilus so that the contrast medium suspension could pass freely through the liver The infusion pressure varied between 20—30 mmHg

The injection into the hepatic arteries was made by cannulating the celiac artery and opening the inferior caval vein as was done in the injection into the portal vein Other branches of the celiac artery than those leading to the liver were closed and in most cases the portal vein was also cut The infusion pressure for the new-born was 100 mmHg on an average and for the young and the fullgrown sheep 130 mmHg

The injection into the hepatic vein was made by introducing a cannula into the draining point of the hepatic veins and by closing the inferior caval vein both from the distal and the proximal side of the hepatic veins. Both the portal vein and the hepatic artery were opened for a free retrograded flow throughout the liver The infusion pressure was 20 mmHg on an average

The combined injection into the portal vein and the hepatic art ry was made by cannulating these vessels, as has been explained before and by open ng the inferior caval vein. The infusion pressures were the same as in the separate injections

When the injections had been made all the blood vessels leading to the liver were ligated in order to avoi l leakage and the liver was cautiously removed and fixed *en bloc* in plenty of 10 % buffered neutral formalin for at least 10 days.

The general picture and the preliminary estimation of the filling grade of the vascular pattern was obtained by contact radiography of the whole liver and of the 2 mm serial sections prepared of the liver on Kodalith Contact Photomechanical Film (20 lines per mm) (Fig 3) In the radiography a Machlett AFG 50 roentgen tube with a focus of 1.5 mm in diameter and equipped with a 1 5 mm thick beryllium win low was used. It was operated at 30 kV the focus-film distance being 1 meter The geometric blurring was under these conditions 3 micra. From th evenly filled areas slices w re chosen for contact microradiography by embedding them in a paraffin-beeswax solution (4 1) and cutting them into 150—500 micra sections. The sections were placed in contact on the photographic emulsion (Kodak Spectroscopic Plate 649 E or Kodak Maximum Resolution Plate 1000 lines per mm) The radiography was done with the same roentgen equipment and voltage the focus-film distance being 0.5 m (geometric blurring 0.5—1.5 micra) The examination of the radiograms and the measurings of the different structures were made with a microscope equipped with a calibrated micrometer scale Part of the sections were radiographed for stereoscopy by tilting the section in the horizontal plane in both directions (43, 66) The examination of the stereopairs was made under a double microscope (Fig 4) In a ldition to the microradiograms, 5—7 micra paraffin sections were prepared of the radiographed sections and were stained with hematoxylin and Van Gieson s stain for a histological examination (Fig. 5)

RESULTS

MICROANGIOGRAPHY OF THE LIVER IN THE FETAL AND NEONATAL SHEEP

Filling grade of the vascular pattern

In all cases a good filling to the sinusoidal level could be seen. After the vein injections the visualization of the sinusoids was occasionally so effective that it rendered the examination of the smaller both afferent and efferent vascular structures more difficult. It could also be seen that the filling grade of the vascular pattern varied to some extent in the different regions of the liver. In the separate injections into the arterial as well as the venous side both vascular systems were filled, although the smaller arterial capillaries were best visualized when the injection had been made through the hepatic artery. Not in a single case was found any signs of overfilling pointing to extravasation of the contrast medium or rupture of the capillaries.

Portal vein

In the fetal and the spontaneously born lambs the branching out of the portal vein into terminal branches happens very soon, the smallest branches having a diameter of about 30 micra (Fig. 6). From these arise at a right or slightly sharp angle at 30—50 micra intervals, inlet venules, which drain into the sinusoids and which are 20—50 micra wide and 15—25 micra long. The inlet venules branch out immediately into the nearest sinusoids. The number of inlet venules decreases on making a more proximal examination of the portal vein and from the branches larger than 90 micra no direct draining into the sinusoids can be seen. The draining into the sinusoids occurs more often through the terminal twigs than through the inlet venules (Fig. 6).

Hepatic artery

The hepatic artery, the branching of which follows that of the portal vein, is, in the fetus and in the spontaneously born of a diameter of approximately 1 1.5—1 2 of the portal vein (Fig. 7, 8). The branches of the artery are found to terminate 1) in the sinusoids, 2) around the bile ducts forming the periductal arterial plexus and 3) directly in the smallest branches of the hepatic vein.

The branches draining into the sinusoids have a diameter of 7—15 micra. The terminal arterioles are generally long and thin and branch out more sparsely than the corresponding portal veins (Fig. 8, 9). As the branches of the portal vein drain at quite a regular distance pericentrically from the hepatic vein, the arteries are seen to drain both pericentrically as regards the central vein (Fig. 7, 9, 10) and also into the sinusoids quite close to it (Fig. 11, 12). In some microradiograms the artery is seen to end in the inlet venule beginning right from the portal vein (Fig. 8, 13). The arterial branches of different territories are chiefly with one

another non-anastomosing end arteries (Fig 14) Anastomoses are, however occasionally seen between the terminal branches (Fig. 15)

The bile duct accompanying the portal vein and the hepatic artery is lined with the periductal plexus, the vessels of which, 4—60 micra in size are richly anastomosing with one another (Fig. 16) The arteries anastomose with the periductal plexus, which in turn sends thin branches, 4—10 micra in size into the sinusoids (Fig 16 17) The draining into the sinusoids is more frequent through the periductal plexus than directly through the hepatic artery Branches from the periductal plexus draining into the portal vein cannot be found.

Arterial branches passing the sinusoids and draining into the smallest branches of the hepatic vein are quite often seen in the fetus and in the new-born both in injections into the hepatic artery and into the hepatic vein (Fig. 18, 19 20) The diameter of these arterio-venous anastomoses varies from 10—20 micra. No anastomoses can be found with hepatic veins larger than 120 micra.

Direct arterio-portal anastomoses are not found in connection with any injection.

Hepatic vein

Both in the fetus and in the spontaneously born the sinusoids, at 10—25 micra intervals, drain into the smallest branches of the hepatic vein, the central veins, the diameter of which is 20—40 micra. The central veins soon unite into larger branches, into which the sinusoids still enter directly although more sparsely (Fig 21, 22) Into veins of a greater diameter than 120 micra the sinusoids do not drain directly

Sinusoidal network

In the fetus the sinusoidal network is shaped as if arranged into lobules, although it is often difficult to distinguish the limits (Fig 23) If the filling of the sinusoids has occurred through the portal vein or through the hepatic artery these are seen to form the limits of the lobule and the central vein is seen in the middle (Fig 9) If the filling has occurred through the hepatic vein the picture is reverse the central veins surrounding the portal space (Fig. 12)

The sinusoids are irregularly shaped and appear to be short, their diameter varying from 15—20 micra and their length from 10—20 micra, and no distinctly distinguishable radial tendency between the periphery and the centre of the lobule can be found. The distance between the portal and central venule the translobular distance, is about 150—200 micra.

In the new-born the lobular structure can be more distinctly distinguished, and in the sinusoids some radiality as well between the periphery and the centre, the translobular distance being 250—400 micra (Fig. 24)

Regardless of their venous or arterial origin all the sinusoids are alike. The structure of the blood vessels in the different lobes of the liver is similar

MICROANGIOGRAPHY OF THE LIVER IN THE YOUNG AND THE FULLGROWN SHEEP

Filling grade of the vascular pattern

In all the injections into the venous side there was a good filling up to the sinusoidal level, as there was in the fetal and the neonatal period, too. The periductal plexuses are mostly also visualized in these injections, but the rest of the arterial system rarely In the arterial injections the visualization of the sinusoids varied and the filling of the veins, when it could be observed, was moderate. No signs of overfilling could be seen.

Portal vein

In the liver of the young and the fullgrown sheep the terminal branches of the portal vein are longer than in the fetus and the spontaneously born and the final branching out occurs gradually (Fig. [illegible]) The perilobular veins are 40—60 micra in diameter and from these proceed at 150—400 micra intervals, inlet venules draining into the sinusoid. The diameter of these inlet venules is [illegible]0 micra and the length 3[illegible] micra, and they are found up to branches of the portal vein 140 micra in size. No direct draining from vessels of larger calibre through the inlet venules, into the sinusoids is seen. The number of inlet venules arising from the terminal branches is greater than in the fetus and the spontaneously born, in which the draining into the sinusoids chiefly occurs through the terminal twigs. The inlet venules branch out both into the periphery of the lobule and directly towards the centre. From the peripheral branches the radial sinusoids are seen to proceed at a right angle towards the centre (Fig. [illegible])

Anastomoses, passing the sinusoids, between the portal vein and the hepatic vein are not found nor any between the different branches of the portal vein.

Hepatic artery

In the young and the fullgrown sheep the hepatic artery traversing the portal canal is approximately ¼ of the corresponding portal vein (Fig. [illegible]) and from it branches proceed 1) into the sinusoids and 2) into the periductal plexuses. In the young sheep is occasionally found direct draining into the beginning of the hepatic vein, in the fullgrown this is not to be seen. The larger arterial branches of different territories do not anastomose with one another.

The diameter of the branches draining into the sinusoids is 7—1[illegible] micra. As was already found in the fetus the terminal arteries, in the fullgrown sheep as well, branch out less than the corresponding portal veins (Fig. 6) In some preparations two terminal arterioles are found to run parallel and to anastomose with one another (Fig. 2[illegible]) At the interlobular level the terminal arterioles from different territories anastomose with each other (Fig. 28)

Table 2. *Summary of the microangiographic findings in different age groups*

	Portal vein				Hepatic artery			
					Terminal distribution to			
Age	termination	mainly draining into sinusoids through	size of perilobular branches (μ)	size of biggest branch giving inlet venule (μ)	sinusoids directly	through periductal plexus	in lobulus	origin of hepatic vein (size of anast. in μ)
Fet. [illegible]	stunted	terminal twigs	30	90	few	mainly	periph. to cent.	often (10—20)
[illegible]—6 days	stunted	terminal twigs	30	90	few	mainly	periph. to centr.	often (10—[illegible]0)
[illegible]—4 months	gradual	inlet venule	50	140	few	mainly	periph.	occasionally (10—[illegible]0)
1—1½ yrs	gradual	inlet venule	60	140	few	mainly	periph.	never

There are no anastomoses between the larger vessels. The arteries draining into the sinuses near the central vein, observed in the fetus, are not found, but the draining occurs into the sinusoids located peripherically from the central vein.

The richly anastomosing periductal plexus accompanies the hepatic artery and the portal vein in the portal canal. The calibre of the vessels of the pl xus varies from 4—60 micra, and it anastomoses both with the hepatic artery (Fig 29) an l through the smallest vessels with the sinusoids (Fig 30) The arterial communication with the sinusoids is more frequent through the peri luctal plexus than through the hepatic artery Any lirect communication between the plexus an l the portal vein is not to be seen

Anastomoses, passing the sinusoids, between the hepatic arteriole and the hepatic venule which are often found in the fetus and th spontaneously born are occasionally observed in the young sheep (Fig 31) and in the full grown sheep these are not found in any in jection at all

Direct arterio-portal anastomoses cannot either in the young or in the fullgrown sheep, be produced with injections from any direc tion. In Figure 3? a thin arterial branch is seen lraining into an inlet venule proceeding from the portal vein

Hepatic vein

In the fullgrown sheep the sinusoids, at 15—.. micra intervals, at an almost right angle drain into the central veins, which have a diameter of 50—70 micra (Fig 33) There is also draining from the sinusoids into the larger veins, but veins with a greater diameter than 600 micra lo not communicate directly with the sinusoids. The separate branches of the central an l sublobular veins are longer than in the fetus and their uniting into larger veins happens more gradually than in the fetus.

Sinusoidal network

In the fullgrown sheep a listinct lobular structure is made out in which the periphery of the lobule has rather clearly marked limits

			Hepatic vein			Sinusoids		
size of peri-lobular branches (μ)	size of vessels of peri-ductal plexus (μ)	proportion to corre-sponding portal vein	origin	size of central vein (μ)	size of biggest vessel joining sinusoids (μ)	diameter (μ)	length (μ)	Trans-lobular distance (μ)
—15	4—60	1 1.5—1 2	stunted	20—40	120	15—20	10—20	150—230
5—15	4—60	1 1.5—1	stunted	20—40	120	15—20	10—20	250—400
5—15	4—60	1 3	gradual	50—70	600	11—15	30—50	400—500
5—15	4—60	1 4	gradual	50—70	600	11—15	20—60	400—.00

and the sinusoids turn radially towards the centre. If the injection has been made with the flow through the portal vein the sinusoids are seen to converge towards the central vein (Fig. 34). If the injection has been made against the flow through the hepatic vein the picture is reversed the sinusoids converging towards the portal vein (Fig. 35). The sinusoids are quite regular in shape and tapering their diameter being 11—18 micra and their length 30—50 micra. As a result of the length of the radial sinusoids the translobular distance in the adult (400—500 micra) is greater than in the fetus and the spontaneously born in which the radial sinusoids are short.

The sinusoids leave the terminal portal veins at a sharp angle. Qualitatively all sinusoids are similar to each other as they are in the fetus, too. No differences in the vascular structures between the different lobes of the liver can be found.

In Table 2 is presented a short summary of the microangiographical findings in the different periods of age.

DISCUSSION

METHOD

Many authors have found microangiography to be useful and a method possessing many advantages when studying the architecture of the capillary level in vitro (6 7 11 16 95 96) Its advantages, as compared to the conventional histological examination is the thickness of the section to be examined, whereas the general picture of the vascular structure depthwise gets clearer particularly when utilizing a three-dimensional microradiographic technique (43 66) By means of the technique of preparing serial sections, which is rather painstaking to realize it is, however possible to reconstruct a good three-dimensional picture of the vascular pattern of the liver In most studies the hepatic vascular pattern has been infused with different stains. With a careful injection technique in which a too liberal filling of the sinusoids, obscuring the capillaries, has been avoided, it has, in up to 100 micra cleared sections, been possible to study the vascular pattern (8) The advantage of microangiography as regards the stain injection technique is that it is possible to get an exact picture of the vascular structure from the thicker sections. A good general picture of the hepatic vascular pattern is also obtained by the injection-cast method but the high viscosity of the injectable substances makes a complete filling at the capillary level difficult (73 8) and this method is better suited for studying the larger vessels.

Since the result obtainable by microangiography is dependent on several interacting factors, the possibility of artefact is great (95) For this reason an attempt must be made to standardize the procedure and apply it in each case in such a way that the results are reproducible

In this study earlier by us obtained results have been put to use on the basis of which was found that the 10% Chromopaque® and Micropaque® particle suspensions, when injected under controlled conditions at +37°C with a pressure corresponding to the physiological pressure of the blood vessel and the anesthetized animal dying during the injection completely filled the renal capillaries having a diameter of 5 micra (109) In the present study it was possible to fill the vessels as far as to the hepatic arterial capillaries with a diameter of 4 micra (Fig 4, 13 3?) Of the particle suspensions used in other microangiographic examinations of the liver $BaSO_4$ is the most common The concentration of the infused suspensions has been the same as in this study (21) or greater (14 93)

When comparing infusion times of different duration it has been found that the renal capillaries are fairly well filled in 20 minutes already although an insignificant flow of the contrast medium still occurs even after 2—3 hours (72) In the present study the infusion time was 1 hour on an average after which the flow was only trifling. In the microangiographical examination of the liver made by Reeves *et al* (93) the infusion time was 20 min., in other corresponding examinations no exact infusion times have been given.

In microangiographical examinations the

suitable infusion pressure has generally been considered to be the physiological pressure of the blood vessel (9). Reeves et al (93) have infused both the arteries and the veins of the liver with the low pressure of 20 mmHg achieving a good filling. In the present study could not be found that the injection into the arteries, made with a higher pressure had caused any overfilling or too liberal a filling of the sinusoids, which would have made the examination of the arterioles or the venules difficult as may happen in stain injections with a high pressure (8).

The preparation of the section to be radiographed the two- and three-dimensional contact radiography and the identification of the findings by means of histological serial sections of the radiographed sections corresponded in principle to the methods, which have earlier been described in literature (7 11 41 43 66 79 81 9).

As has been said above microangiography as applied here is a purely morphological method of study. Even though an attempt would be made to preserve the most physiological conditions possible during the injection the functional status of the blood vessels has, at the end of the procedure changed to such an extent that no conclusions can be drawn from the radiograms of the physiological state of the blood vessels (44 58). Under in vivo conditions it has been possible to apply microangiography to radiographing the vascular pattern of thin objects, such as the ear lobe of the rabbit (12) and thin pre-exposed muscular fibres (97) under various experimental conditions. Since this method is limited only to radiography of thin objects it cannot be realized in studying the liver. Attempts to preserve the in vivo conditions of the hepatic vascular bed for microangiography have been reported. The reactions of the blood vessels to vasoactive substances have been studied from en bloc radiographed livers (61) and from rapidly frozen microradiographed sections (6). The detection of the vessels has ranged from 50 micra upwards.

By means of in vivo made transillumination examinations of the liver (for ref see 10) a dynamic morphological picture is obtained of the hepatic microcirculation but this examination is limited to the surface of the thin edge of the liver and cannot be applied to an examination all through the liver.

MICROANGIOGRAPHY OF THE PRE- AND POSTNATAL HEPATIC CIRCULATION

General

The studies dealing with the microcirculation of the liver in the fetus are not very numerous (75 78 83 103) and in literature no studies are found, in which microangiography has been applied to clarify the fetal or neonatal microcirculation. Although the morphology of the microcirculation in most mammals has been clarified by means of different methods, the studies of the hepatic circulation in the sheep both in the pre- and the postnatal period, have consisted primarily of macroscopic angiographic examinations (8 57 69 87).

In this study it has been possible to see that the microvasculature of the liver in the sheep has, before birth, developed rather a good way towards its fullgrown state although both quantitative and to some extent also qualitative differences between the fetus and the full grown sheep could be established (Table 2)

Portal vein

The portal vein s simple and fast distribution into terminal branches in the fetus, which has earlier been presented by others in man (75 83) could in this study be established in the microradiogram of the sheep s fetus. As the liver grows and its functional activity increases the terminal branching also increases and the vascular design becomes more com

plex. In the fetus the terminal portal branches are of a smaller calibre than in the fullgrown sheep and the draining into the sinusoids occurs mainly through the terminal twigs, whereas it in the fullgrown sheep chiefly occurs through the inlet venules. In the full grown sheep inlet venules were found, which turned both towards the periphery of the lobule and towards its centre. The peripheral large sinusoids were similar to those earlier observed in examinations made by means of stain injections (33) and in microradiography of the rabbit (93). In the fetus the draining of the inlet venules is also more terminal and only branches turning directly towards the centre were found.

The number of inlet venules is reduced both in the fetus and in the adult when proceeding proximally in the portal system, and from the larger branches no direct draining into the sinusoids is found. This corresponds to the organization of the circulation found both in man and in several mammals (39). In the large portal canals marginal distributing branches, proceeding in the same direction with the portal vein and from which inlet venules would arise (33) were not seen in this study. The inlet venules had their origin in the terminal, either at a right or sharp angle branching vessels, which corresponds to the observations made in the adult rabbit by Reeves *et al.* (93).

Hepatic artery

The calibre of the hepatic arteries in the fetus and in the spontaneously born sheep was relatively large in regard to the corresponding portal vein ([illegible]) which has been considered a characteristic feature of the fetal internal vascular pattern of the liver in man (83). In the adult human being the hepatic artery has, in earlier studies, been found to be [illegible] of the corresponding hepatic vein (18, 83). In the present study the corresponding proportion in the fullgrown sheep is [illegible], i.e. only slightly smaller than in the fetus. The high proportion in the fetal period is probably explained by the inactivity of the fetal portal blood circulation (83) even though the flow in the hepatic arterioles also is very sparse (78).

In flow studies of the liver has, in the full grown dog and cat as well as in the adult human being been found that the arterial flow is approximately [illegible] of the portal vein circulation (51) a proportion which is considerably higher than what the calibre proportion of the corresponding vessels has been found to be (18, 83). This shows that on the basis of the surface areas of the cross sections of the vessels cannot in this study be drawn any far reaching conclusions about the relative flows in the fetal and the adult period. In addition the injection technique in which an attempt has been made to fill all the vessels, is so violent that the physiological status of the lifetime has changed in the final result.

In the portal canal was, both in the fetus and in the fullgrown sheep, found one larger and several differently sized, both with one another and with the larger artery anastomosing smaller branches. The latter corresponded to the periductal plexus described by Reeves *et al.* (93) in the microangiographic examination of the rabbit's liver, where the size of the vessels ranged from 8—100 micra. There are also authors, who only call vessels of capillary size located in the portal space periductal plexus and the other vessels actual hepatic arteries (39, [illegible]). Generally there is agreement about the anastomoses between the differently sized arterial branches.

At the lobular level was in the fullgrown sheep occasionally found two equally sized parallel hepatic arterioles anastomosing with one another, as has also been found in some other mammals (82, 94, 108).

In the sheep the arteries of the different territories were both in the pre- and the postnatal period, with one another non-anastomosing end arteries up to the lobular level, as Glauser (49) has proved in the adult human being. At the terminal interlobular

l ~el it was foun l that the art rial bran hes ana tomosed betw n the different t rritories, a fin ling which hardl correspon l to the juxtahepatic (80) an l the subcapsular (103) anas omoses f und in man an l in some mammals.

The terminal listribution of th h patic artery in the fetus liff re l in two ways from the correspon ling ne in th fullgrown she p

1) In the f tu the lraining int the sinusoi ls occurre l l th into the periphery an l the centre of the lobule whereas in the fullgrown sheep only a peripheral lraining was found. Concerning the fullgrown she p this fin ling can be compared to the observa tions ma le by others in many diff rent test animal (4 73 77 82, 93) in which the tran lobular arteries lescril l by Elias and P tty (37) have not l en possible to fin l. Neither has it been possible to fin l these art rioles in th rabbit fetus (8) which contradicts the present stu ly One reason for the diff rence in observations can be the liff rence in t st animal

2) In fetal peri l were f und rather numerous terminal branches of the h patic artery passing the sinusoi ls an l draining into the beginning of the hepati vein which could not be f und in the a lult Concerning the fetus no antecedent to this observation can be foun l in literature On the other hand, no art rio-venous anastomoses have in most stu li s been f und in the a lult

The translobular arterioles an l the arterio-ven us anastomoses found in the sheep s fetus strive t pass the sinusoids, whi h evi l ntly illustrates the insignificance of the arterial blood irculation as the liver receives oxygen rich blood through the umbilical irculation The closed hepati arterioles in dye injection studies of human fetuses (6) an l of the transilluminated f tal liver of rabbits (78) also verify the lifference in hepatic oxygen supply between th pre and postnatal period.

The periductal largely anastomosing plexus was already well level ped in the fetus and it communicated both with the hepati artery an l with the sinusoi ls The "internal r ts" connecting the plexus and the portal vein which several authors have described in among others, the cat th rat the rabbit an l in man (37 63 73 82, 93) were not f un l in the microra liograms either in th pre or the postnatal peri d In all ra liograms the branches from the plexus w re found t en l in the same way as the other arterioles

In both the fetus an l the fullgrown sheep was obs rve l that the arterial communication with the sinusoi ls is m re frequent through the periductal plexus than through the arteries lirectly which correspon ls to the observations ma le by earlier auth rs in the fullgrown rabbit an l rat (82, 93)

Direct arterio-portal anastomoses, whi h have been foun l in th frog an l in many mammals un l r a vital microscope (15, 64 98 10) an l in examinations by means of injec ti ns (2 73, 82, 93) were not seen in a single microra liogram of the sheep s f tus or the fullgrown sheep In the microangiographies of the liver ma le by Chendlerovitch (21) in man, the rabbit the rat and the pig it has not been possible either to show arterio-portal anastomoses. Neither has Elias (3) in his extensive histological stu lies seen any

The arterio-portal anastomoses, seen in earlier studies, have generally been located near the terminal end of the portal vein and the hepatic arterial system and the assumption of their importance in the control of the portal pressure (8) has been impossible to confirm by physiological examinations (51) The arterioles, draining into the periphery of the lobule ended, in this study either lirectly in the sinusoids or in the junction of the terminal branches of the portal vein an l the sinusoids, in the inlet venule The latter draining of the arteries can be compared to the functional "arterio-portal anastomosis" ending close to the beginning of the sinusoids, which was found by McCuskey in fullgrown frogs, rats, mice and rabbits (77) as well as in the rabbit fetus (8) under a vital microscope It has not been possible to prove actual structural

anastomoses in this study as was also the case in McCusker's study.

The observations of anastomoses between the larger vessels are in the earlier studies incidental and on the basis of this study it can, with certainty be established that they are not to be found in sheep of any age.

In the microangiographic examination where the section to be examined is rather thick, the structures being one on top of the other may misleadingly produce the impression of their being united, if the examination is not made both two- and three dimensionally or if the results is not confirmed by means of histological serial sections. In this respect the observation made in the microangiography of the liver in the fullgrown rabbit (25) of the arterio-portal anastomosis cannot be regarded as completely reliable.

The injection technique in which the injections are made simultaneously both from the arterial and the venous side has in some studies been considered important for showing the details of the hepatic vascular pattern and particularly the arterio-portal anastomoses (73 82). It has, however in the single stain injections into the hepatic artery by Mitra (8) and in the contrast medium injections int the portal vein by Reeves *et al* (93) been possible to visibly fill both the arterial an l the venous side. In this study was, by experimenting, obtained the same result both with the singl and the double injection technique after which the main part of the injections was made as single.

Somebody may suspect that the arterio-venous anastomoses found in this study are arterio-portal, but as can be seen from Figures 18, 19 and 20 the veins are typical hepatic veins into which the sinusoids drain at frequent intervals.

Hepatic vein

In both the fetus and the fullgrown sheep the sinusoids drained into the smaller branches of the hepati vein which corresponds to the observations made in the rabbit (8 93) th adult human being an l in the dog (35) As in man (83) the beginning of the hepatic vein was blunt and stunted in the sheep's fetus compared to the more finely distributed branching found in the fullgrown sheep. In the fetus, however could not be foun l any draining of the sinusoids into the large hepatic veins, as has been seen in man (83). The microradiogram of the liver of the fullgrown sheep is comparable to the one seen of the rabbit (93) in which the sinusoids at frequent intervals drain into the central veins and the sublobular veins.

Sinusoidal network

The differences seen between the fetus and the fullgrown sheep are comparable to those foun l in the rabbit (78). In the fetus the sinusoids were tortuous an l the distinct radial turning between the centre and the periphery of the lobule seen in the a lult could not be found. The extravascular fetal hemopoietic focuses an l the numerous intersinusoidal sinusoids have been given as reason for this tortuosity (78). The diameter of the fetus sinusoids was somewhat greater on an average than in the adult, but the size of the lobule smaller as has earlier been seen in man and in the rabbit (75 78). The sinusoids being arranged aroun l the portal tria l r the central vein in the microradiogram depended on the direction of the injection (9 40) and in this study coul l not be shown any fixated portal or fetal (19 32, 75 83) nor any lobular arrangement of the sinusoids, as suggested by Kiernan (63). In the same indivi lual all the sinusoids were alike regardless of whether they were in communication with the arteries or with the veins.

During the fetal period differences have been found between the left an l the right half of the liver in the hemopoiesis (42) in the distribution of th umbilical and the portal

level it was found that the arterial branches anastomosed between the different territories, a finding which hardly corresponds to the juxtahepatic (80) and the subcapsular (103) anastomoses found in man and in some mammals.

The terminal distribution of the hepatic artery in the fetus differed in two ways from the corresponding one in the fullgrown sheep

1) In the fetus the draining into the sinusoids occurred both into the periphery and the centre of the lobule whereas in the fullgrown sheep only a peripheral draining was found Concerning the fullgrown sheep this finding can be compared to the observations made by others in many different test animals (34 71 77 82, 93) in which the translobular arteries described by Elias and Petty (34) have not been possible to find Neither has it been possible to find these arterioles in the rabbit fetus (78) which contradicts the present study One reason for the difference in observations can be the difference in test animal

2) In *fetal period were found rather* numerous terminal branches of the hepatic artery passing the sinusoids and draining into the beginning of the hepatic vein which could not be found in the adult Concerning the fetus no antecedent to this observation can be found in literature On the other hand, no arterio-venous anastomoses have in most studies, been found in the adult

The translobular arterioles and the arterio-venous anastomoses found in the sheep's fetus strive to pass the sinusoids, which evidently illustrates the insignificance of the arterial *blood circulation as the liver receives oxygen* rich blood through the umbilical circulation. The closed hepatic arterioles in live injection studies of human fetuses (62) and of the transilluminated fetal liver of rabbits (78) also verify the difference in hepatic oxygen supply between the pre- and postnatal period

The periductal largely anastomosing plexus was already well developed in the fetus and it communicated both with the hepatic artery and with the sinusoids. The "internal roots" connecting the plexus and the portal vein which several authors have described in among others, the cat the rat the rabbit and in man (34 63 73 82 93) were not *found in the microradiograms either in the* pre or the postnatal period In all radiograms the branches from the plexus were found to end in the same way as the other arterioles.

In both the fetus and the fullgrown sheep was observed that the arterial communication with the sinusoids is more frequent through the periductal plexus than through the arteries directly which corresponds to the observations made by earlier authors in the fullgrown rabbit and rat (82, 93)

Direct arterio-portal anastomoses, which have been found in the frog and in many mammals under a vital microscope (15 64 98 107) and in examinations by means of injections (2, 43 82, 93) were not seen in a single microradiogram of the sheep's fetus or the fullgrown sheep In the microangiographies of the liver made by Chenderovitch (21) in man *the rabbit the rat and the pig it has not been* possible either to show arterio-portal anastomoses. Neither has Elias (3) in his extensive histological studies seen any

The arterio-portal anastomoses, seen in earlier studies, have generally been located near the terminal end of the portal vein and the hepatic arterial system, and the assumption of their importance in the control of the portal pressure (82) has been impossible to confirm by physiological examinations (51) The arterioles, draining into the periphery of the lobule ended, in this study either directly in *the sinusoids or in the junction of the terminal* branches of the portal vein and the sinusoids, in the inlet venule The latter draining of the arteries can be compared to the functional "arterio-portal anastomosis" ending close to the beginning of the sinusoids, which was found by McCuskey in fullgrown frogs, rats, mice and rabbits (67) as well as in the rabbit fetus (78) under a vital microscope. It has not been possible to prove actual structural

SUMMARY

The microarchitecture of the hepatic circulation in the 39 fetal, neonatal, young and fullgrown sheep was examined by means of microangiography. The contrast medium was, under standardized and controlled conditions, injected separately into the portal vein, the hepatic artery and the hepatic vein while the anesthetized test animal died just before or during the procedure. The fixated liver and the thick serial sections of the liver were radiographed for the preliminary examination. Chosen slices were embedded in paraffin-beeswax and cut for general and stereo-contact microradiography. For confirmation of the observations histological sections were further prepared of the radiographed sections.

Before birth the picture of the microvascular pattern of the liver was in general, as regards its structural principles, almost similar to that of the fullgrown sheep. In addition to the quantitative differences there were also some qualitative ones, which besides being based upon the differences in size of the liver probably are based on the different functional activity of the liver in the pre- and postnatal periods.

1) Portal vein. In the fetus and the spontaneously born the distribution of the portal vein into terminal branches occurred sooner than in the fullgrown sheep and the general picture in the fetus became stunted compared to the portal vein of the fullgrown sheep. The diameter of the perilobular branches was 30 micra in the fetus and 50—60 micra in the young and the fullgrown sheep. Both in the fetus and in the fullgrown sheep the draining into the sinusoids occurred only from the terminal branches, either through the terminal twigs or through the inlet venules at the lobular level. In the prenatal period the draining occurred more often through the terminal twigs and changed in the postnatal period to occur chiefly through the inlet venules. There were no anastomoses between the different portal branches or between the portal vein and the hepatic vein.

2) Hepatic artery. In the fetus and the new born the hepatic artery, in proportion to the corresponding portal vein, was somewhat larger than in the fullgrown sheep. In the fetus and the fullgrown sheep the hepatic artery was in communication with the richly anastomosing periductal plexus, proceeding in the same portal canal, the diameter of which vessels was 4—60 micra in all periods of age. The draining into the sinusoids from the periductal plexus through vessels having a diameter of 4—10 micra was more frequent than directly from the hepatic artery, the diameter of which perilobular branches was 7—15 micra. The hepatic arteries of the different territories only anastomosed at the terminal lobular level, at which was also occasionally found, in the fullgrown period, two parallel branches of the hepatic artery.

In the fetal and the neonatal period was seen rather numerous terminal arterial branches draining both into the sinusoids, located near the beginning of the hepatic vein, and directly into the smaller branches of the hepatic vein, which in the young sheep was incidental and in the fullgrown sheep not

seen in a single radiogram. The diameter of the arterio-venous anastomosis was 10—20 micra. The passing of the sinusoids has been believed to depend on the insignificance of the arterial circulation as the liver receives oxygen rich blood through the umbilical circulation.

No arterio-portal anastomoses were found either in the pre- or in the postnatal period. A part of the arteries drained into the inlet venules arising from the portal venule.

3) Hepatic vein. In the fetus the sinusoids drained as far as into vessels with a diameter of 170 micra and in the fullgrown sheep into vessels with a diameter of 600 micra at frequent intervals, which typically distinguished the hepatic vein from the portal vein. In the fetus the size of the central veins was 20—40 micra and in the fullgrown sheep 50—70 micra. The smaller branches of the hepatic vein were shorter and united into larger sooner than in the adult, due to which the hepatic venous system seemed more stunted in the fetus than in the adult.

4) Sinusoidal network. In the fetus the diameter of the sinusoids was 15—20 micra and the length 10—20 micra, the corresponding dimensions in the fullgrown sheep were 11—18 micra and 30—50 micra. The translobular distance was 150—250 micra in the fetus, 250—400 micra in the spontaneously born and 400—500 micra in the fullgrown sheep. The sinusoids of the fetus were irregular in shape and the distinct radial turning of the sinusoids between the centre and the periphery of the lobule found in the fullgrown sheep could not be seen. Because of the foregoing the limits of the lobule could not either be as clearly distinguished in the fetus as in the fullgrown sheep. The picture of the portal and the hepatic lobule, both in the fetus and in the fullgrown sheep, was outlined in accordance with whether the injection had been made through the hepatic vein or through the portal vein.

No differences in the vascular structure were found either in the fetus or in the fullgrown sheep in the same individual between the different lobes of the liver.

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FIGURES

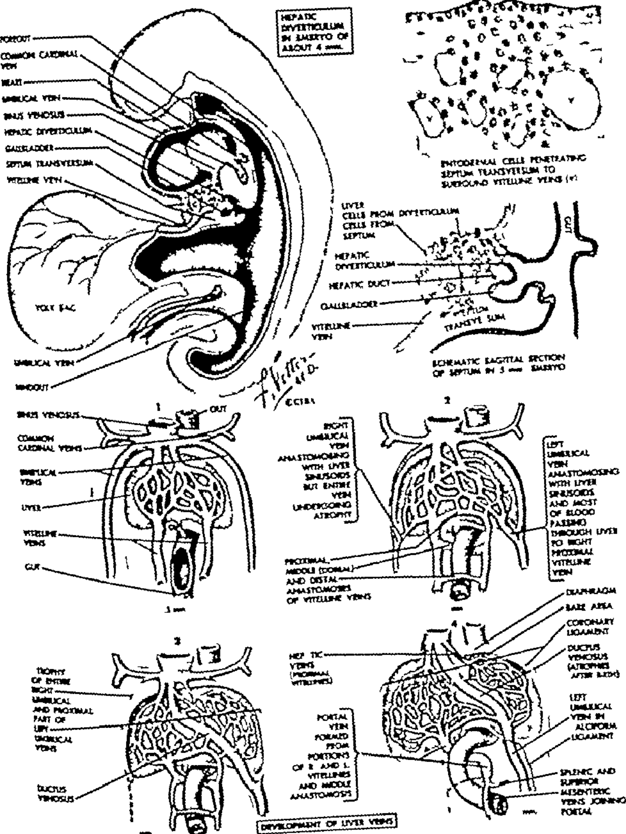


Fig. 1. Embryology of the liver. (Copyright the Ciba Collection of Medical Illustrations by Frank H. Netter M. D. published by Ciba Pharmaceutical C

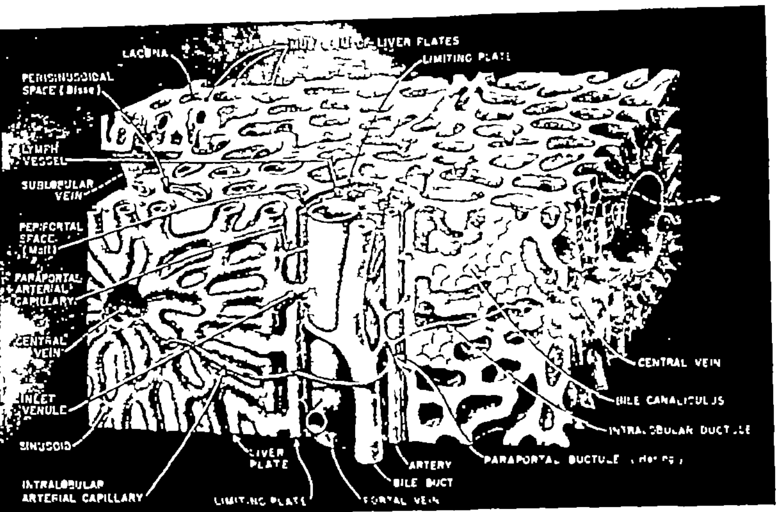


Fig 8 Microvasculature of the li er (Reproduced, with permission, from Elia H & Sherrick, J C.: *Morphology of the l ver* Aca lemic Press, New York, London, 1960.)



Fig. 3. Overall pattern f the liver f the newborn sheep (ge 1 da weight 3.3 kg). Injection through hepatic artery. Radiogram of 2 mm section.



Fig 4 a and b Stereo-pair microradiograms of the same 150 μ section of the fetus (weight 1.4 kg) The capillary of the peribiliary plexus crosses the hepatic artery and does not join it. Section through umbilical vein. × 100



Fig 5 One of the serial histologic sections of the microradiographed section in Fig. 4. In the serial sections the capillary (arrow) of the periductal plexus does not join the artery (A). Injection dye Micropaque®, Van Gieson stain. X 100.



Fig 6 Terminal branch of the portal vein in the fetus (weight ..7 kg). The narrowing of the smallest branches is rapid and the draining into the sinusoids occurs more frequently through the terminal twigs (T) than the inlet venules (I). Injection through umbilical vein. Microradiogram of 150 μ section. X 100.



Fig Termin l bra hes f the hepatic rtery (A) nd the portal ein (P) i the fetus (eight –9 kg) The ratio bet ee th rterial nd the poorl lled portal vessels is 1:– The rteri le branches out t long l tera l l j ins the si usoid f ff the central venule (V) t the peri hery f the lobule I jection through hepatic artery Microra iogram f 150 μ section. X 160.



F g. 8 Hepatic rtery (A) nd port l ei (P) in the same port l canal i the newborn sheep (ge 1 da weight 3.3 kg) The ratio between the calibres of th essel is 1 1.5—1 – One arteriole ca be seen t t the si usoids near the port l rigi (arrow) I jection through hepatic rtery Microradiogram f 1.0 μ section. X 63.



Fig. 9. Hepatic arterioles in the interlobular space in the fetus (weight 1.? kg). Arrows indicate branches to the sinusoids. Injection through umbilical vein. Microradiogram of 150 μ section. X 63.

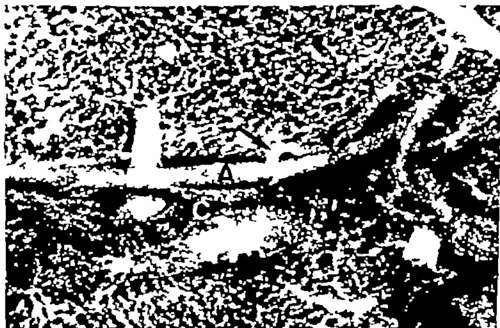


Fig. 10. Hepatic arteriole (A) joins the sinusoids (arrow) at the periphery of the lobule in the fetus (weight 2. kg). A capillary branch (C) of the arteriole sends one branch back into the same vessel. Injection through umbilical vein. Microradiogram of 150 μ section. X 100.

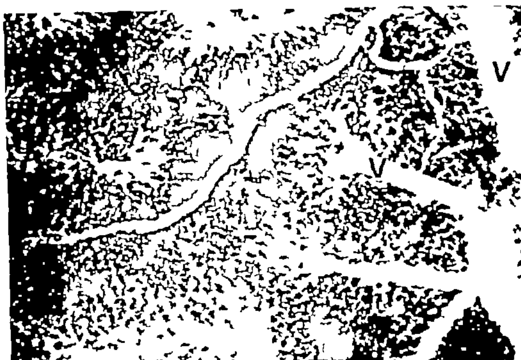


Fig 11 H patic [illegible] the f tus (eight [illegible]9 kg) T [illegible] les (rrow) open in t the sinuso [illegible] th hepatic [illegible] ule (V) The area near the hepatic enules are better [illegible] th [illegible] t l tract where th arteriole runs int [illegible] nd enters the periphe al [illegible] ject throu h hepatic rtery Microradiogram f 150 μ section. X 65.



Fig 12 Hepatic rteriole (A) in the fetus (weight 1.9 kg) entering sinusoids near the central vein (V) The sinusoids near the hepatic venules are well visualized and the impression f the portal lobule (P) here the sinusoids converge from the hepatic venules to the portal tract, lso comes through I jection through hepatic vein. Microradiogram of 150 μ section. X 100



Fig 13 Arteriole (arrows) follows the portal vein (P) in the newborn sheep (age 1 da weight 3.3 kg) and enters th origin of the sinusoids. I jection through umbilical vein. Microradiogram of 150 μ section. X 160.



Fig 14 Overall pattern f the terminal ends f the hepatic artery in the newborn sheep (ge 1 day weight 3.9 kg) Anastomoses between different arterioles could not be found. Injection through hepatic artery Microradiogram f 150 μ section. X 23.



Fig 19 Hepatic arteriole (arrow) communicates with the hepatic venule (V) in the fetus (weight 2.9 kg) Injection through hepatic artery Microradiogram of 150 μ section. X 100



Fig 20 Hepatic arteriole (arrow) communicates with the hepatic venule (V) in the newborn sheep (age 1 day weight 3.0 kg) The other arterioles join the sinusoids. Injection through hepatic artery. Microradiogram of 150 μ section. X 100

Fig. 21. Origin of the hepatic vein in the fetus (weight 1.0 kg). Injection through hepatic vein. Microradiogram of 1.0 µ section. X 100.



Fig. 22. Hepatic veins in the fetus (weight 1.2 kg). The large vein has no direct connection with the sinusoids, which enter the smaller ones. Injection through hepatic vein. Microradiogram of 150 µ section. X 22.

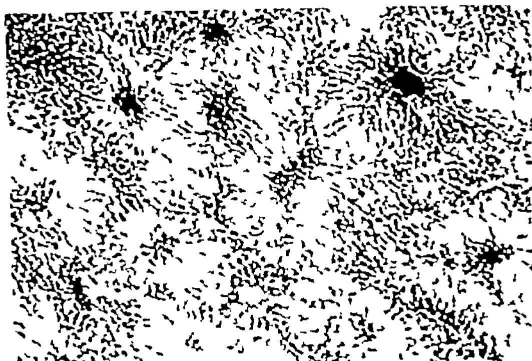


Fig 23 Sinusoids in the fetus (weight [illegible]) The limits of the lobules are not clearly distinguishable. Injection through umbilical vein. Microradiogram of 1_0 μ section. X 63.



Fig 24 Sinusoids in the newborn sheep (age ½ day weight _8 kg) The portal veins surround the hepatic lobule (black areas) Injection through umbilical vein. Microradiogram of 150 μ section. X 63.

Fig 25 Terminal branch f the portal vein in the fullgrown sheep (ge 1½ yrs weight 28 kg) The subdivision int the smallest branches is gra lual and the draining into the sinusoids occurs mostly through the inlet ven les (I) Injection through portal vein. Microradiogram f 150 μ section. X 100



F g 26 Terminal branches f the hepatic artery (A) and the portal el (P) in the fu grown sheep (ge 1½ yrs, weight 30 kg) The ratio between the calibres f the arterial and the poorly visualized portal vessels is 1 3. Some capillaries (C) of the peribiliary plexus are filled and join the hepatic artery Injection through hepatic artery Microradiogram f 150 μ section X 63.

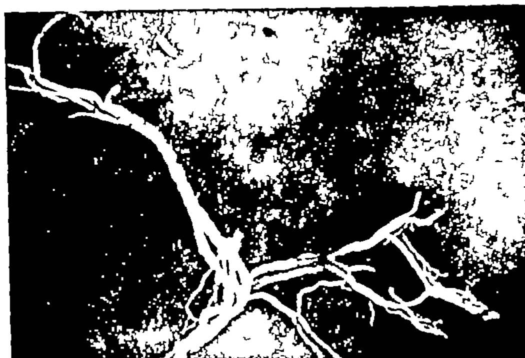


Fig. 2[?] Terminal distribution of the hepati[c a]rtery in the you[n]g sheep ([a]ge 4 months, weight 19 kg). Two arteries of the same size are in the portal canal and are connected with each other. Some capillaries of the peribiliary plexus are [a]lso visualized. The sinusoid[s] are not filled with the dye. I[n]jection through hepatic artery. Microradiogram [o]f 150 μ section. X 63.



Fig. 22. Hepatic interlobular arterioles with the periductal plexus in the fullgrown sheep ([a]ge 1½ yrs, weight 30 kg). The terminal branches from different territories anastomose. The visua[l]ized sinusoids originat[e] from the periductal plexus and are directed towards the centre [o]f the lobule. I[n]jection through hepatic artery. Microradiogram [o]f 150 μ section. X 63.

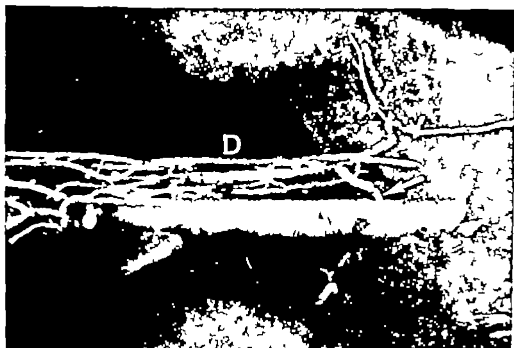


Fig 29 The periductal plexus (D) is connected (arrow) with the hepatic artery (A) in the young sheep (age 4 months, weight 19 kg) The sinusoids are not visualized. Injection through hepatic artery Microradiogram of 100 μ section. X 63.

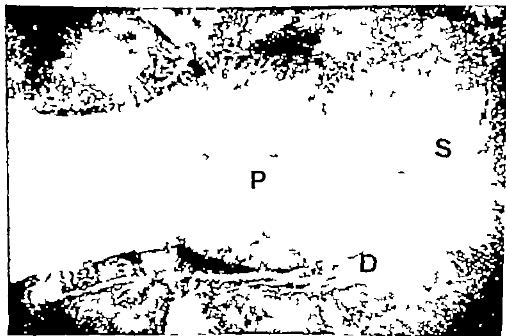


Fig 30 Periductal plexus (D) and portal vein (P) in the young sheep (age 4 months, weight 19 kg) *The plexus joins the sinusoids (S) but not the portal vein. Injection through portal vein* and hepatic artery Microradiogram of 150 μ section. X 63.



Fig. 35 Sinusoids con erge from th hepatic veins t the port l vein formi g the picture of the portal lobule in the fullgrow sheep (age 1 yea weight .3 kg) I jection through hepatic vein. Microradiogram f 150 μ section. X 62.

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ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 234 1973

COW'S MILK ALLERGY PREVALENCE AND MANIFESTATIONS IN AN UNSELECTED SERIES OF NEWBORNS

BY J W GERRARD J W A. MACKENZIE,
N GOLUBOFF J Z. GARSON AND C. S MANINGAS

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM

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From the Department of Pediatrics University Hospital
University of Saskatchewan, Saskatoon, Saskatchewan, Canada

COW'S MILK ALLERGY
EVALENCE AND MANIFESTATIONS IN
I UNSELECTED SERIES OF NEWBORNS

by

J W Gerrard J W A MacKenzie N Goluboff
J Z. Garson and C S Maningas

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Several studies have been carried out to try to determine the prevalence of cow's milk allergy (CMA) in infants, but before reviewing these it seems appropriate to clarify the meaning of the term "allergy" as used in this article.

The term "allergy" was originally introduced by von Pirquet (51) to indicate the change in reaction to foreign substances which occurred with the development of hypersensitivity. The two cardinal features which he emphasized were 1) on first exposure to the allergen there was no untoward reaction on the part of the patient or animal, but on a second or subsequent exposure, there was, and 2) that this reaction showed evidence of hypersensitivity-the reaction usually occurred with a shortened latent period. The examples of the allergic response that he gave manifested, in modern terminology both immediate and delayed type hypersensitivity states. We have used the term "allergy" in relation to cow's milk with the same connotation that von Pirquet did, implying that the response of the subject to cow's milk is a "changed reaction" differing in this respect from the reactions of normals, whose reactions to cow's milk are indistinguishable from their reactions to other foods. In using the term "allergy" we have also implied, as von Pirquet did, that the subject manifests evidence of hypersensitivity.

With the discovery that IgE plays an important role in hypersensitivity states (26) many have equated allergy with IgE mediated responses. We have not used the term allergy in this limited context nor have we implied any specific immunological response.

Because we do not know how allergic reactions to cow's milk are mediated, we might have used instead the phrase "illness induced by cow's milk". This phrase is noncommittal and is well accepted in other fields. We discuss, for example, illnesses induced by the streptococcus, recognizing that while the streptococcus can cause illness directly by invasion of the tissues, it can also cause illness indirectly by leading to the deposition of antigen-antibody complexes and the activation of complement, (2) as well as by stimulating the development of antibodies which cross-react with heart muscle (28). It is probable that some if not all, of the adverse reactions to cow's milk antigens are similarly mediated by a variety of immunological mechanisms. For this reason it would have been appropriate to use "cow's milk induced illness". We have however elected to use the phrase "cow's milk allergy" (CMA) as this is in keeping both with common usage and with the term as originally used by von Pirquet. We expect that it will soon be possible to use more specific terms and to indicate into which of the categories outlined by Gell and Coombs (16) the various manifestations of CMA fall.

With regard to previous studies on the prevalence of CMA, Clein (7) stated that approximately 6% of babies had CMA but he did not give any details of his findings. Collins-Williams (8) studied its prevalence in 3 000 babies from his own practice. He first excluded from his survey all babies with "major allergies" and all babies referred to him by physicians or brought to him by mothers because they were thought to be allergic. He found the prevalence of CMA in this truncated series to be 0.3% only 9 of the 3 000 babies were found to have CMA. Eight of the babies presented with vomiting or diarrhea, an additional baby was irritable and cried a great deal. No baby had respiratory symptoms and none had eczema. His series therefore is not representa-

tive of the normal population for it excluded two of the major manifestations of CMA. Bachmann and Dees (3) followed up a consecutive series of 403 unselected babies and found only four (1%) with proven CMA These babies had varying combinations of "rashes" diarrhea and frequent colds only one baby wheezed. In the group as a whole during the first two years of life 25 had spells of diarrhea and vomiting 62 had rashes of one kind or another 32 had frequent colds, and 40 wheezed. It would seem that approximately 20% of the babies studied by them had allergic problems, though in only a small proportion could cow's milk be incriminated. These findings contrasted with their experience with a group of 172 infants under the age of two years, referred for allergic studies (4). One hundred and nine of these children were found to be allergic and of these, 33% had CMA. Had 33 of the allergic children in their series of unselected normal babies been similarly allergic to cow's milk, the prevalence of CMA in this group would have been approximately 7% Mueller and his colleagues (35) also tried to determine the prevalence of CMA in a series of babies, but as they had no control over the management of the babies, they were unable to shed any light on the incidence of CMA. They concluded that a study could be productive only if those in charge had control over the care and management of the babies. It was in the light of these observations that the present study was undertaken.

This study was made with the following objectives.

1 To determine the prevalence of CMA as well as of allergic problems in general in a consecutive series of babies born at the University Hospital, Saskatoon.

2. To try to determine if it is possible by taking a careful history from the parents when the baby is only a few days old, to predict which baby is likely to develop allergies, and in particular CMA.

3 To determine the prevalence of the various manifestations of CMA and

4 To identify the foods to which babies are most commonly allergic.

MATERIAL AND METHODS

Most of the mothers admitted to the University Hospital are admitted under the care of obstetricians; their babies are usually referred to paediatricians for immediate and continuing care A few babies are delivered by family physicians such babies, provided no complications arise in their care and management usually remain under the care of the family physician. Three of the paediatricians on the staff at the University Hospital look after the majority of obstetrical deliveries these three, together with one family physician who has developed a particular interest in paediatric problems, agreed to participate with the chief author in this project. All four are generalists, none confines his interest to any one subspecialty All were, and are very much aware of the chief author's interest in food allergy and specifically in CMA but none had any preconceived ideas or bias, save that one in particular was keen to demonstrate the relative infrequency of CMA. All accepted the diagnosis only after repeated elimination and challenge. It was agreed to include in the survey all babies, provided their parents were agreeable for whom the authors provided primary care. Five parents opted out of the study the remainder agreed to participate, though a few of the latter were reluctant to comply with formula changes suggested later to determine whether a baby was or was not allergic to cow's milk.

Case histories

These were taken by two nurses, previously trained in history taking, on prepared proforma which included the following data. 1) the age, marital status and ethnic origin of the parents, 2) the prevalence in the parents and siblings of a history of eczema, hay fever asthma, urticaria, recurrent bronchitis, allergies to food and drugs, enuresis and recurrent

headaches; 3) the attitudes of the parents and siblings to milk, i.e. whether they liked or disliked it. The parents were also asked which, other things being equal they would prefer to drink—milk or water. If a parent disliked milk he was asked the reason for this dislike and was given the following alternatives to choose from. that it is too expensive too fattening distasteful or causes vomiting abdominal discomfort, diarrhea or constipation or that it is avoided for other reasons.

Choice of formula

No attempt was made to persuade a mother to choose one formula rather than another though in a few selected instances, the paediatrician concerned may have recommended that the baby be breast fed. No baby was placed on a soya formula, anticipating that he might be allergic to cow's milk.

Consent for participation in the study

Just before the history was taken, the nurse explained to the mother concerned the purpose of the study and asked her if she would be agreeable to participate in it. She indicated to her that if the baby were thought to be allergic to milk it would be necessary to provide changes in formula and food intake, and then later to challenge him twice with the formula which had appeared to upset him. The nurse also explained that she would contact the mother at regular intervals.

Dietary history

A record was kept of the ages at which new foods were offered the baby for the first time.

Additional information

When each baby reached his first birthday a second medical record was completed containing details of visits to doctors for illness and of admissions to hospital. When he was two years old a third medical record was completed which included details of all the illnesses which the child had had in his second year of life.

Manifestations of an allergic reaction

A baby with one or more of the following symptoms was considered a candidate for CMA and investigated accordingly

1 Respiratory A persistent or recurrent rhinorrhea, bronchiolitis or asthma.

2. Cutaneous: A persistent or recurrent pruritic dermatitis usually involving one or other of the following the cheeks, chin, forehead flexures or even the whole body

3. Gastrointestinal. Vomiting and/or diarrhea of a persistent nature not due to any demonstrable pathology

The above are not the only manifestations that have been or can be ascribed to CMA in the infant, but they are the commonest and as such deserved the closest attention. Cow's milk may reputedly cause colic, irritability hyperactivity enuresis or frequency of micturition and constipation, but it is not certain that these are allergic disorders, nor is their identification always possible in a small infant. No attempt was therefore made either to identify them or to determine whether they were or were not caused by Cow's milk feedings.

Follow-up examinations

After discharge from hospital, usually on the fifth day of life, the babies were followed by their paediatricians in exactly the same manner as their other patients. They were in addition, contacted by the nurses involved in the project at the ages of 2 and 4 weeks, at 3 6, and 12 months, and again at the 15th, 18th and 24th months. Babies who had symptoms that might be ascribed to allergy were contacted much more frequently home visits were made by the nurse who also arranged for them to be seen by their doctors in their offices. Their care and management were discussed at regular conferences. Initially all the paediatricians, as well as the nurses, attended these conferences, but as the numbers under review increased the conferences were held with the paediatricians individually the nurses being in attendance.

Table 1 *Distribution of the babies under their respective paediatricians and the prevalence of CMA*

Paediatrician	All babies	Babies with CMA	Percentage with CMA
JWAM	394	31	7.9
NG	196	12	6.1
JZG	113	9	8.0
CM	71	4	5 6
JWG	13	3	23.0
Total	787	59	7.5

The management of a baby thought to be allergic to milk

A baby thought to have CMA was taken off his cow s milk formula and was offered a soya formula instead. When necessary he was also taken off all other foods. If his symptoms settled he was then challenged either with his original cow s milk formula or with homogenized cow s milk. If his symptoms returned he was again taken off milk and dairy products. When his symptoms had subsided he was rechallenged a second time Only if his symptoms returned after two separate challenges was he considered to be allergic to cow s milk. If the baby appeared to be sensitive to soya, i.e if his symptoms did not subside when he was taken off cow s milk and placed on a soya formula, he was offered either an alternative commercially available soya preparation or placed on a meat base formula. Babies allergic to one food are frequently allergic to other foods. In such instances it is not possible to demonstrate an allergy to cow s milk unless the baby s diet can be limited to one or two simple foods on which he is absolutely symptom free. Not all mothers, particularly when the child s symptoms were relatively mild, were prepared to subject their child to such a rigorous regime. In these instances the etiology of the suspected allergy was not identified. In all instances a record was kept of the foods to which the baby appeared to be allergic, though only in the case of cow s milk was this confirmed by repeated challenge.

Many babies during the course of the study developed eczema, recurrent rhinorrhea, bronchiolitis and/or asthma, but not in response to cow s milk. In many cases it was possible to identify the allergen and to note that the eczema, for example was due to citrus fruits or to contact with a "baby oil" but in other instances it was not. When the final analysis was made, babies were placed in one of the following categories:

1 Normal. Such babies remained free from any allergic diseases during the course of the study

2. Suspect allergies. Such babies had, at one time or another symptoms that are often ascribed to allergy e.g. eczema, urticaria, a recurrent rhinitis or asthma, but in no instance was there objective evidence that cow's milk was a causative factor

3 Milk allergies: These babies had allergic problems precipitated by cow's milk, confirmed by two repeated challenges. Many of the babies, in addition, appeared to be allergic to other foods.

RESULTS

803 babies were eligible for admission to the project. 5 were excluded because their mothers did not want to participate 4 could not be traced, 2 died at the ages of 3 and 15 days of complications of prematurity and 5 moved out of Saskatchewan soon after discharge from hospital and so were lost to the study The remaining 787 consecutive babies were included in the study 59 (33 boys and 26 girls) were found to be allergic to cow s milk. The distribution of the babies among the paediatricians and the prevalence of CMA in their respective patients are shown in Table 1

The prevalence of CMA among the patients of the individual paediatricians did not vary appreciably except in the case of JWG who provided primary care for only a few selected patients expected to have problems, though not necessarily of an allergic nature.

The influence of breast feeding on the prevalence and development of CMA

The number and percentages of all babies, as well as of babies with CMA brought up on breast milk and formula, is given in Table 2. It can be seen that the proportions do not vary significantly. There is no evidence from this data that babies brought up on the breast for a few months only are protected from CMA, though had 10 of the babies been brought up on the breast and not been offered cow's milk before the age of 12 months, they might not have developed CMA, for by 12 months of age they were no longer allergic to cow's milk.

Manifestations of cow's milk allergy

The symptoms with which the babies presented were as follows:

Recurrent diarrhea	24
Repeated vomiting	13
Persistent colic	12
Eczema	27
Recurrent rhinorrhea	18
Recurrent bronchitis	10
Asthma	7

Colic was not used as a diagnostic symptom but it was frequently associated with allergic problems, and when this was the case it was recorded. In 25 instances the baby presented with only one symptom. In the remaining 34 instances he presented with two or more e.g., with recurrent rhinorrhea and diarrhea. It should again be emphasized that the above symptoms all developed while the baby was receiving a cow's milk formula, cleared when he was taken off this formula, and recurred on two separate occasions when he was once more given either his original formula or cow's milk. Eczema was the commonest mode of presentation, followed by diarrhea.

Twenty-four babies presented with diarrhea. In 3 the diarrhea was associated with macroscopic blood loss in the stool, in 16 with obvious allergic problems such as eczema, rhinorrhea or recurrent bronchitis. The associated allergies, as well as the diarrhea, cleared when cow's milk was removed from the diet, and returned when it was reintroduced. We therefore assumed in these instances that both the respiratory and the gastrointestinal tracts were allergic to milk, and not that the baby had a dual pathology a respiratory allergy and an intestinal lactase deficiency. Eight babies had no associated allergy. In two of these the diarrhea persisted while the baby was on a lactose free soya formula, and it was assumed that the baby was sensitive to both soya and cow's milk. The six other children who developed diarrhea on cow's milk may have developed secondary lactase deficiencies, but we do not think that they had primary lactase deficiencies, for in our experience jejunal biopsies in babies with diarrhea due to CMA rarely have absent lactase activities (33) although these may be reduced. Our experience is in keeping with Liu's (32) who found that babies with diarrhea due to CMA had flat lactose tolerance tests when first seen, but that these became normal when the baby was taken off cow's milk, becoming flat once more when cow's milk protein was introduced into the diet.

One baby in the series was a candidate for a primary lactase deficiency. This baby developed diarrhea while on the breast alone he also developed a rhinorrhea. The mother was drinking cow's milk in moderate amounts. Knowing that foods taken by the mother can cause allergic reactions in a baby on the breast (18), and knowing that in this instance a previous sibling had developed diarrhea both while on the breast and on soya, we advised the mother to stop taking cow's milk and dairy products. This she did, and the baby's symp-

Table 2. *Frequency of breast and formula feeding*

	All babies		Babies with CMA	
	Total	%	Total	%
Breast fed	374	47.5	26	44
Formula fed	413	52.5	33	56

Table 3 *Sensitivities to foods other than cow s milk in babies with CMA*

D = diarrhea, V = vomiting, C = colic, E = eczema, R = rhinorrhea, B = bronchitis, A = asthma

	D	V	C	E	R	B	A	No. of cases
Soya	4	2		2	2	1	1	10
Wheat	2		1	1	1			5
Rice	1	1		2	1			4
Barley		1	1	1				3
Orange	1			11				12
Tomato	1	1		3				4
Beef	1							1
Chicken		1						1
Lamb	2		1					3
Veal	1							1
Pork				3				3
Egg				6		1		7
Totals	13	5	3	28	5		1	54

toms subsided, only to return promptly when she again drank cow s milk. At a later date the baby was given cow's milk to drink and again promptly developed *diarrhea and rhinor* rhea, together with bronchitis. In this instance a primary lactase deficiency was a reasonable provisional diagnosis, but subsequent studies indicated that the baby tolerated lactose in breast milk and that he had a true gastrointestinal and respiratory milk allergy being so sensitive to cow s milk that he reacted adversely to traces of cow s milk or cow s milk products in breast milk.

Associated food allergies

Soya. A soya formula was offered 51 of the CMA babies. The formula was tolerated by 40, refused by 1 and caused, in the remainder diarrhea in 4 vomiting in 2, eczema in 2, rhinorrhea in 2, bronchiolitis in 1 and asthma in 1 A fifth of the babies with CMA were allergic to soya formulas. The refined newer formulas were generally used. We noted in 5 instances that when one proprietary preparation was not tolerated, a second one was, *suggesting either that the soya protein had* been denatured in one and not in the other or that other ingredients in the formula had caused symptoms.

Goat s milk. One child who had developed rhinorrhea and vomiting on cow's milk, and rhinorrhea, vomiting and diarrhea on soya, tolerated goat s milk well.

Babies with CMA are often allergic or develop allergies to foods other than cow s milk (18). The additional foods to which babies with CMA appeared to be sensitive together with the reactions to these foods, are given in Table 3 We would suspect that allergies might develop to many other foods were they to be given sufficiently often or in sufficient quantity Whether some systems are more likely than others to react to any given food, e.g., the skin to citrus fruits and the gastrointestinal tract to wheat, we cannot say but such a possibility warrants further study It is possible also, that the foods which cause eczema in the baby may cause other symptoms, asthma for example, in the older child.

Table 4 *The number of babies free from allergies, with suspect allergies and with CMA*

Category	No.	%
Babies free from allergies	457	58.1
Babies with suspect allergies	271	34.4
Babies with CMA	59	7.5
Totals	787	100

Children suspected of having allergies but not to cow s milk

As already indicated, the babies included in this survey were consigned to three categories, depending on whether they were free from allergies, were suspected of having allergies to factors other than to cow s milk, or had CMA (Table 4).

The babies with suspect allergies" comprised two main groups: those whose allergies were simple and easily elucidated, often without the paediatrician s help, and those whose problems were more complex. Babies with simple problems included those who developed eczema, e g., whenever they were given orange juice, or urticaria when given peanut butter There were 238 such babies. Babies with more

complex problems were less numerous, there being only 33 such babies. They tended to have symptoms which could well have been due to infections, e.g. recurrent rhinorrhea, bronchitis and spells of loose stools. The etiology of these symptoms remained undetermined, either because it was not possible to arrange an adequate elimination diet, or because foods appeared to be etiologically unimportant.

In the "suspect allergy" group as a whole sensitivities to the foods indicated in Table 5 were noted. We did not try to identify allergens other than foods but noted that detergents caused eczema in 6 and wool caused eczema in 1 dog dander caused asthma in 1

Age at onset of symptoms

The age at which the diagnosis of CMA was made and confirmed varied greatly from child to child, but as a careful record had been kept of the child's age when he first developed symptoms, it was possible to relate the onset of symptoms to the age at which he was first exposed to cow's milk, whether this was given as formula or as a supplement. One baby developed symptoms before he was given cow's milk, he developed diarrhea and rhinorrhea when he was 24 days old and still on the breast alone his symptoms settled when his mother stopped drinking cow's milk and they recurred both when his mother began to drink it again and later when he himself was given cow's milk to drink. We concluded that he was allergic to factors in cow's milk appearing in his mother's breast milk.

Table 5 *Reactions to foods noted in babies suspected of having allergies to foods other than to cow's milk*

E – eczema, D – diarrhea, V – vomiting, U – urticaria, B – bronchitis

	E	D	V	U	B
Orange	13	8	6		
Eggs	10	2	3	1	
Rice	7	2	4		2
Tomato	10	2		1	
Banana	4	2	3		
Oats	3	3	2		1
Vitamin preparations	7				
Chocolate	4			1	
Pear		1		1	
Wheat	1				
Barley	2	2			
Potato	1				
Peanut butter				1	
Totals	62	22	18	5	3

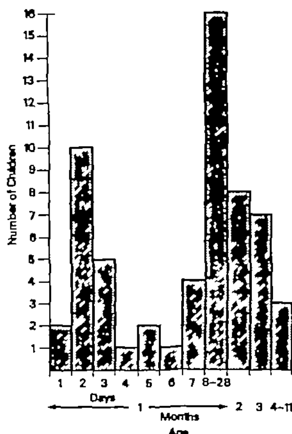


Fig 1 Introduction to cow's milk and onset of symptoms.

The ages at which symptoms first developed are given in Figure 1 It can be seen that 17 (28%) of the babies developed the first signs of eczema, rhinorrhea, vomiting and diarrhea within 3 days of being given a prepared formula derived from cow's milk, and that 25 (41%) did so within 7 days. Symptoms developed in other babies at greater intervals but there certainly was no need in nearly half the instances for the baby to have prolonged exposure to cow's milk in order to develop an allergy to it.

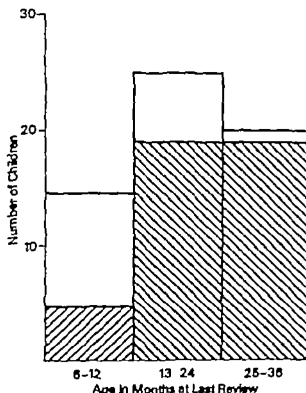


Fig 2. Recovery from cow's milk allergy ☐ Still have CMA ☐ recovered from CMA.

Recovery from or persistence of CMA

Four babies were lost to follow-up· one of these was adopted out of the study the other three left the province and could not be traced the remainder were followed for between 12 and 36 months, when grant support was curtailed. From Figure 2 it can be seen that 17 of the 59 children appear to have lost their sensitivity to milk, 10 of these (17% of the total) lost their sensitivity by the age of 12 months a further 6 during the second year of life and only 1 in the third year 42 of the children 38 of whom are more than one year old, are still sensitive to cow s milk 3 of these can take a little low fat (2%) milk but large amounts cause a return of rhinorrhea, bronchitis, asthma or eczema. Three of the children who still have CMA now refuse to drink milk. Our experience with these and other babies indicates that it is not possible to predict which baby will and which will not outgrow his CMA. The most exquisitely sensitive baby may later be able to drink cow s milk and remain absolutely symptom-free. Conversely the more mildly affected may continue to have CMA. We suspect that once a baby can tolerate milk he will usually remain free from CMA but of this we are not certain for we have seen infants with CMA who later appeared to be able to tolerate cow s milk but who when they were older developed colds and bronchitis with or without wheezing and who again responded to the elimination of milk and dairy products from their diet.

Visits to doctors for illness during the first year of life

The number of visits made by mothers with babies to physicians for check-ups during the first year of life depends on many factors such as the socio-economic status of the parents, the place of the baby in the family (mothers attending more frequently or regularly with their first than with subsequent babies) and on the availability of well baby clinics where immunizations are carried out. Rather than note how many times during the first year of life a baby attended a doctor s office since this would include routine examinations and inoculations, we decided to record only the number of visits for illness. Six hundred and nine babies were available for review at the age of one year

It can be seen from Table 6 that during the

Table 6. The number of visits to physicians for illness during the first year of life

Visits to doctors for illness	Babies free from allergies		Babies with suspect allergies		Babies with CMA	
	No.	%	No.	%	No.	%
0	109	37 4	83	31.9	15	23 8
1	108	37.3	58	22.3	7	12.1
2	35	12.0	49	18.8	12	20 7
3 or more	39	13 4	70	26.9	24	41 4
Totals	291		260		58	
Average number of visits per patient		1 14		1.89		2.89

Table 7 *Admissions to hospital during the first year of life*

Admissions to hospital	Babies free from allergies		Babies with suspect allergies		Babies with CMA	
	No.	%	No.	%	No.	%
0	250	85.0	214	82	42	72.0
1	38	13.0	38	14.5	13	22.4
2	2	.068	6	2.3	2	3.4
3	1	.034	1	.38	—	—
4	—	—	—	—	1	1.7
Totals	291		260		58	

first year of life allergic children visited their doctors on account of illness more frequently than did children who were free from allergies. Children with CMA visited their doctors on account of illness twice as often as those who had no allergic problems. This increase is highly significant ($\chi^2_{(2)} = 107.8$, $P < 0.0001$).

Admissions to hospital during the first year of life

Admissions to hospital depend on the severity of the illness, the availability of beds, medical insurance, etc. In Saskatchewan beds are readily available and as virtually every person has hospital coverage, sick children tend to gain admission to hospital readily. The number of children under study and admitted to hospital during the first year of life is given in Table 7. Children with CMA were admitted to hospital significantly more frequently than those free from or with suspect allergies ($\chi^2_{(2)} = 11.84$, $P < 0.005$).

Table 8 *Number of children under study followed until they were two years old*

	Babies free from allergies		Babies with suspect allergies		Babies with CMA	
	Total		Total	%	Total	%
Follow up completed	112	24.5	73	26.9	32	54.2
Follow up not completed	345	75.5	198	73.1	27	45.8
Total	457		271		59	

Table 9 *The prevalence of certain common infections and disorders during the first two years of life in the children under study*

Illness or Disease	Children (112) free from allergies		Children (73) with suspect allergies		Children (32) with CMA	
	No.	%	No.	%	No.	%
Frequent colds	22	19.6	23	31.5	15	47.0
Ear infections	4	3.6	5	6.8	7	21.9
Bronchitis	3	2.6	5	6.8	2	6.2
Asthma	0	—	6	8.2	2	6.2
Spells of vomiting	1	0.9	3	3.1	5	15.6
Spells of diarrhea	5	4.4	12	16.4	8	25.0
Spells of abdominal pain	2	1.8	—	—	2	6.2
Eczema	—	—	22	30.0	7	22.0
Urticaria	—	—	3	4.1	1	3.1
Rashes	5	4.4	16	22.0	9	28.0
Rubeola	12	45.5	5	39.7	1	34.3
Roseola	23		12		3	
Rubella	1		4		2	
Mumps	4		1		0	
Varicella	11		6		5	

Second year follow-up

At the time of the second year follow-up, 217 children were available for study: these children had reached the age of two and had not moved away from Saskatoon. The numbers in each group are given in Table 8.

It can be seen that contact was kept with a much greater proportion of babies with CMA than with babies free from allergies or with suspect allergies. The reason for concentrating on this group of babies was that we were keen to learn whether babies with CMA did or did not lose their sensitivity to milk.

Illnesses during the first two years

A careful record was kept of the illnesses experienced by the children during the first two years in order to determine whether children with CMA or with suspect allergies were more or less prone than their non-allergic counterparts to develop certain diseases. The results are detailed in Table 9.

There is a greater prevalence of asthma, eczema and urticaria in the babies with CMA

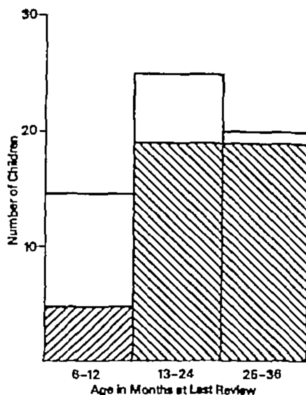


Fig 2 Recovery from cow's milk allergy □ Still have CMA, □ recovered from CMA.

Recovery from or persistence of CMA

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Visits to doctors for illness during the first year of life

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1	108	37.3	58	22.3	7	12.1
2	35	12.0	49	18.8	12	20.7
3 or more	39	13.4	70	26.9	24	41 4
Totals	291		260		58	
Average number of visits per patient		1.14		1.89		2.89

Table 11 *Prevalence of major allergies in the mothers of babies who were normal, who had suspect allergies and who had CMA*

	Normals		Suspect allergies		CMA	
	No.		No.	%	No.	
Urticaria	53	11.6	35	12.9	14	23.7
Hay fever	27	5 9	34	12.5	8	13.7
Asthma	12	2.6	9	3.3	4	6.9
Eczema	39	8.5	38	14.0	1	20.3
Totals	457		271		59	

Allergies were significantly more common in the mothers of babies with CMA than in the mothers of normals $\chi^2_{( )}$ = 30.63 $P < 0.005$ in the mothers of babies with CMA than in the mothers of babies with suspect allergies, $\chi^2_{(4)}$ = 10.84 $0.025 < P < 0.05$ and in the mothers of babies with suspect allergies than in the mothers or normals $\chi^2_{( )}$ = 19 4 $P < 0.005$ The differences were significant when tested with complete independence $\chi^2_{(8)}$ = 41 43, $P < 0.005$

siblings of three groups of children (Tables 10–12). These family histories were taken when the baby was first included in the study be fore it was known whether he would or would not have allergies. These allergic diseases were most prevalent in the parents and siblings of children with CMA, they were least prevalent in the close relatives of the children free from allergies.

Attitudes towards milk

There was no evidence of an increased antipathy towards milk in the parents of children with CMA from earlier studies we had ex pected that there would be (18).

Twenty-three per cent of the mothers, 8.7% of the fathers and 3 7% of the siblings disliked milk (Table 13) The mothers disliked it significantly more frequently than did the fathers ($P < 0.001$) and the parents significantly more frequently than did the siblings ($P < 0.001$).

The commonest reason given for not drink ing milk was that its taste was unpleasant. Allergic individuals, in our experience, often have unexplained and capricious likes and dislikes, refusing to eat foods for no very obvious reason. In some instances, as became apparent

Table 12. *Prevalence of major allergies in siblings of babies who were normal, who had suspect allergies, and who had CMA*

	Normal		Suspect allergies		CMA	
	No.	%	No.	%	No.	%
Urticaria	15	5.9	9	6.8	3	7
Hay fever	5	1.9	5	3.8	3	7
Asthma	9	3.5	7	5.3	1	2
Eczema	26	10.1	20	15.1	1	29
Totals	255		132		42	

There were significantly more allergies in siblings of babies with CMA than in those of normals $\chi^2_{(2)}$ = 13 4 $P < 0.005$. The differences between the three groups were significant when tested with complete independence. $\chi^2_{(8)}$ = 22.08 $P < 0\,005$

when the children in this survey were followed up (three of the children with CMA later refused to drink cow s milk) individuals may grow to dislike the foods to which they are allergic, though the reverse also obtains. We suspect that the greater prevalence of an antipathy towards milk among mothers is a sequel of the greater prevalence of allergies in this group Eczema ($P < 0.005$) and urticaria ($P < 0.001$) as well as food and drug allergies ($P < 0\,001$) and migraine ($P < 0.001$) were sig nificantly more prevalent in the mothers than in the fathers (Table 13).

Table 13 *The percentage incidence of diseases in mothers, fathers and siblings, together with attitudes towards cow s milk*

	Father (N = 787)	Mother (N = 787)	Siblings (N = 429)	Significant differences: Between fathers & mothers	Significant differences: Between parents & children
Eczema	5.45	11.37	13.5	$P < 0.005$	P 0.005
Hay fever	8.63	8.75	3.01		P 0.005
Asthma	2.15	2.92	3.93		
Urticaria	4.82	12.95	6.24	$P < 0.001$	
R. bronchitis	1.38	7.86	5 11	$P < 0.001$	
F&D all	6.97	15 74	11 49	$P < 0.001$	
Enuresis	4.17	2.41	11.84		$P < 0.001$
Migraine	7.35	16.37	2.3	$P < 0.001$	$P < 0.001$
Milk dislike	8.73	22.98	3.71	$P < 0.001$	$P < 0.001$

Table 14 *Reasons given for not drinking cow's milk*
In 28 instances more than one reason was given

Reasons for disliking milk	Fathers (68)	Mothers (181)
Too fattening	8	20
Taste unpleasant	61	143
Causes nausea	4	14
Causes abdominal pain	0	9
Causes diarrhea	1	0
Causes constipation	0	1
Too expensive	4	6
For reasons other than given above	3	3

DISCUSSION

The prevalence of allergies in CMA

When we analyzed our results we were surprised to find that 42% (330/787) of the infants under study had symptoms which might be ascribed to allergy the commonest being eczema or a contact dermatitis. In most instances symptoms were not severe the baby did not become ill nor did he present a diagnostic problem, developing for example, only a mild eczema when given orange juice or when bathed in a proprietary baby oil" However in at least 82 instances, and these included the 59 babies with CMA the etiology of the child's symptoms was more difficult to determine and though we always tried to find the cause of his symptoms, we were not successful in every case. We were, however able to establish by repeated challenge that 59 (7.5%) had evidence of CMA. This figure is much higher than that given by Backman and Dees (3) but for this there is, as already indicated, a valid explanation. We think that our own figure may err on the side of caution, for since closing the study two further cases of CMA have been identified in babies previously only suspected of having allergies.

The relationship between the ingestion of cow's milk and the onset of symptoms

Our earlier studies (18) indicated and our present studies have confirmed that many babies with CMA, approximately 40% in the present series, develop their symptoms within a week of their first exposure to cow's milk. These babies are often also allergic to other foods. If the baby is seen at this time, careful attention to the history will often enable the physician to identify the food or foods to which the child is allergic. Histories taken months or years later when the child is an established asthmatic, are invariably less specific and less helpful. The reaction of the baby to foods is often so prompt (we have seen a baby develop rhinorrhea and a cough after his first bottle of formula) that such babies appear as Dr Park suggested in the case of his own son (37) to be born with CMA

It has been suggested, and this has been put forward as a reason for placing pregnant mothers of babies at risk on hypoallergenic diets (20) that CMA and other food allergies may be acquired in utero and that it is for this reason that some babies react so promptly This may be true in some instances, but we would also expect that early exposure in utero to foreign antigens might lead to tolerance rather than to allergy Moreover sensitivities to the same food are sometimes found in the same family (17) suggesting that food sensitivities may be genetically determined.

The family history

The inquiry made into the prevalence of allergic diseases in parents and siblings suggests not only that allergies tend to run in families, but also that they are relatively common in the population as a whole. It is for the latter reason that it is not possible to identify with any degree of certainty at birth the child who will or will not have allergic problems. The difficulty of prognosticating is compounded by the fact that many allergic parents are unaware that they have allergic disease they may not suspect that an underlying allergy is responsible for a chronic sinus infection or for recurrent attacks of bronchitis. From our earlier studies (18) it would seem that the risk of an infant developing CMA is greatest if a previous sibling had CMA in these circumstances the risk that a subsequent baby will also be aller

gic to cow's milk is 1 3. Should the day come, and we expect that it will, when each individual will have his own allergic profile, more specific advice will no doubt be possible.

The apparent increased prevalence of some allergies, e.g. eczema, urticaria, food and drug allergies and migraine in mothers when compared to fathers, requires further study In infancy judged by our own experience there is not a preponderance of girls with eczema, for of the 59 children with CMA, 15 boys and only 11 girls had eczema. It is a matter of common experience, however that in girls, at least, allergic problems sometimes change with age, appearing for the first time or disappearing at puberty or at the menopause. Pregnancy too may modify allergies, sometimes accentuating and sometimes relieving them (13 55). The data which we have obtained do not indicate whether the apparent increase in allergic disease in the mothers is associated with sex alone, or with child bearing as well.

Another finding brought out by the questionnaire is the very definite difference in the attitudes towards milk of the children and their mothers and fathers. On this occasion we asked parents who disliked milk why they did so. Most said they disliked it because they found it distasteful and for no other reason. Those who like milk must find it difficult to understand why an individual should dislike and sometimes even hate a beverage which, to most, is a bland, palatable liquid. But this is undoubtedly the case. We observed the development of this attitude to cow's milk in three infants with CMA. We suspect that this dislike arises as a conditioned response, the child noting consciously or unconsciously that drinking milk is associated with unpleasant side effects. Such an explanation does not seem too improbable when it is realized that attitudes towards foods are often dictated by pleasant or unpleasant associations.

As there is such a striking difference between the attitudes of men and women towards milk, we cannot but wonder if this attitude towards milk may not have relevance in other fields of medicine, and may not contribute, for example to the diminished incidence of atherosclerosis and coronary heart disease in women (9)

The relationship of allergy to infection

It is often difficult if not impossible to distinguish on clinical grounds the respiratory and gastrointestinal manifestations of an infection from those of an allergy The features are so similar that children whose attacks of asthma start with a cold are sometimes thought to be allergic to whatever infectious agent or agents cause the cold (47). This may be true in a few selected instances (44). Many such children have been given courses of bacterial antigens but with no objective evidence of benefit (27) Other children have been thought to have immunological deficiencies, and have been given regular injections of gamma globulin, but again without demonstrable benefit (14). From our experience it would seem that the cold" itself may be the initial manifestation of the allergic response, and it is for this reason that it is so promptly followed by the attack of bronchiolitis and/or asthma (49). The grounds for suggesting this are that in those instances in which foods precipitate symptoms, if the food is removed from the diet, the child no longer has one cold after another nor do colds, when they occur precipitate attacks of asthma. However as soon as the child is once more given the food or foods to which he is sensitive his repeated attacks of rhinorrhea or asthma return. This response to the reintroduction of the food is sometimes prompt, developing in a matter of hours, and sometimes delayed, occurring only after two or three weeks re-exposure to the food. It is often associated with fever On clinical grounds it is usually indistinguishable from a respiratory infection (23) wheezing is by no means always present. We would agree with Glaser's (19) dictum that the child who has one cold after another has this because of an underlying allergy" and with Hill's (24) comment, the common cold is indeed too common in asthmatic children"

Many paediatricians are unaware of the significance in the infant of repeated colds and attacks of bronchiolitis. Several years may go by before the child develops classical asthma and it is realized that he is an allergic individual. That this explanation is correct is borne out by the finding that 25% to 50% of the children who have bronchiolitis in infancy develop asthma or allied respiratory allergies subsequently (12, 56 57 58) Half the children with bronchiolitis also have elevated serum IgE levels (15) Conversely the adult asthmatic not infrequently has a history of having had attacks of pneumonia or bronchopneumonia in infancy What is surprising is that even when the bronchiolitis has been proved to be viral in origin many such children, 56% in one series (39) develop attacks of wheezing and/or asthma subsequently We suspect that in these cases the respiratory infection brings to light an underlying allergy So whether the attacks of bronchiolitis are or are not associated with a viral or bacterial infection, provided the child has no other disorders such as an immunological deficiency or cystic fibrosis of the pancreas, he may still have an underlying allergic diathesis and, if so, should be studied accordingly Added confirmation is the finding of a positive family history wheezing in the child an eosinophilia or an elevated serum IgE.

From studies carried out by others (38 44) it appears that half the children with this clinical picture will outgrow their asthma. The paediatrician may therefore be tempted to procrastinate. Why treat a child for a disease from which he will recover spontaneously? Approximately half the children, however will develop obvious asthma children with asthma comprise, in the United States of America one third of those with chronic disease (41). For this reason we feel that the significance of repeated attacks of bronchiolitis and bronchopneumonia in infancy should not be missed and an attempt should be made to determine to what the child is allergic This is a simpler undertaking in infancy than at any other age since, at this time the diet and the environment can be relatively easily controlled.

The management of the baby with CMA

Many clinicians, for reasons of which most of us are aware but for which we find it difficult to find an adequate explanation, are reluctant to ascribe a symptom to allergy until all other possibilities have been excluded. In the light of our increased knowledge of gastrointestinal function, this approach needs modification. It is essential to waste no time in establishing the diagnosis and, allergies being so common, it *is wise in the first instance to assume that the* child's symptoms are due to allergy and to treat him accordingly At the same time studies should be carried out to ensure that other rarer but nevertheless important conditions are not being overlooked. If the baby is on the breast and on the breast alone, it is usually wise to keep him on this while looking into the mother s dietary habits, excluding, on empirical grounds, milk and dairy products and other foods, if she is taking them in excess (10 42) If the baby is on cow s milk-derived formula we would recommend first a soya formula, preferably carbohydrate free If this is not tolerated, a hypoallergenic formula, such as Nutramigen or Pregestimil, should be offered Goat s milk is occasionally though not always, tolerated. We feel that it is usually in the baby s best interests to give the formula full strength, for when this is done it usually becomes quickly apparent that the formula is or is not tolerated. If none of the above formulas suits the baby a meat base formula may be offered. We usually place the baby first on a strained meat, for example lamb and glucose (Appendix A). If this is tolerated we then substitute sucrose for glucose and then add, in turn, a fat a calcium preparation and a vitamin supplement. Occasionally a baby reacts adversely to all meats. A formula based on a cereal or a fruit has then to be engineered. In difficult cases, breast milk may be the only food to be tolerated (36, 48) Where there has been delay in recognizing the allergic nature

of the baby's problem, or extreme difficulty in its management, the gastrointestinal tract may have been so extensively damaged that it may need prolonged rest, in which case the baby will require prolonged intravenous alimentation.

The cause of the high incidence of CMA in infants: speculation

If allergic problems due to foods are as common in infants as we have suggested, the absorption of food antigens, particularly in infancy is probably common also That food proteins can be absorbed in antigenic form was first demonstrated using the P-K test. Subsequent studies have confirmed this repeatedly Walzer (54), for example, studied the absorption of fish and egg using sera from individuals highly sensitive to these proteins. He concluded that the absorption of undigested protein was "a normal phenomenon" Heiner (22), more recently using serum from a wheat sensitive patient, has found that wheat antigens are absorbed in 90% of normal adults. That food proteins can be absorbed by allergic individuals is confirmed by the many adverse reactions manifested by such individuals to ingested foods.

75–98% of babies develop antibodies to milk proteins during the first two years of life (21 29 40). Antibodies develop earlier in those brought up on cow's milk and later in those brought up on the breast (30). IgG antibodies begin to appear at one month, peaking at three IgA antibodies appear later develop more slowly and peak at the seventh month (29). The development of antibodies to milk, and presumably to other food proteins, appears therefore to be a natural phenomenon. Their presence suggests that the immune system may play a part in preventing or limiting the further absorption of milk proteins, and in neutralizing the possible systemic effects of this influx of antigenic material (53). Milk antibodies in the form of precipatins appear to be in greatest concentration when milk proteins are causing disease, as in Heiner's syndrome (23)

The key immunoglobulin patrolling the gastrointestinal tract is secretory IgA (6). The newborn is devoid of both serum and secretory IgA (45) and though 30–50% of newborns have IgG mediated antibodies to cow's milk proteins (21 29), the gastrointestinal tract may not be ready to handle a high antigenic load. In diarrheal states, in particular ingested food antigens gain access to the circulation and may even be found in the urine (43). The newborn is virtually devoid of IgE (5), though some may appear in the serum by the age of 6 weeks. It would seem probable that the high incidence of food allergies in the children under study and presumably in North American children as a whole, is due to the presentation of foreign food antigens, particularly of cow's milk protein to babies at ages when they are incapable on immunological grounds, of confining these proteins to the gut. The repeated presentation of these antigens, in comparatively large amounts, to the offspring of allergic parents can be expected to prime not only cells secreting IgG but also in babies susceptible on genetic grounds, those secreting IgE, with the probable development in the latter instance of allergic diseases. Some of these babies can be expected to "outgrow" their allergies between the ages of 9 and 18 months if the absorption of the food antigens in question is reduced by either a reduction of the dietary load or by an increased secretion of the appropriate secretory IgA. That early priming of the gastrointestinal tract may have long term effects is suggested by the findings of Acheson and Truelove (1), that patients with ulcerative colitis are twice as likely as controls to have been given cow's milk during the first month of life

We would anticipate that withholding food antigens and keeping the baby on the breast alone until he is 9 months old might greatly reduce the incidence of food allergies, for by this age the baby's secretory IgA system has matured appreciably the absorption of the foods in question would be reduced, and the stimulus to the secretion of IgE would be less-

ened. It is for reasons such as these that we think there is validity in Glaser's (20) observations that early cow's milk feedings predispose to the subsequent development of allergic problems in children.

Babies with gastrointestinal CMA may be clinically indistinguishable from those with lactase deficiencies. It is in this area that difficulties may arise in establishing a diagnosis. In both disorders the lactose tolerance test may be flat, and in both, diarrhea and failure to thrive occur on lactose containing formulas. Holzel (25) in his review of the sugar malabsorption syndromes, noted that though primary lactase deficiencies were rare secondary lactase deficiencies were common. This being so the diagnosis of lactase deficiency alone is inadequate, for it is also necessary to identify the cause of the deficiency to find out whether it is primary postinfectious, gluten induced or due to some other cause. Among the important causes of a lactase deficiency as the careful but rarely quoted work of Liu (32) has shown is gastrointestinal milk allergy In the babies which she studied, the lactose tolerance tests were flat while the babies were on formulas containing cow's milk proteins, rising to normal when cow's milk proteins were excluded from the diet, but becoming flat again when they were reintroduced. Gastrointestinal function may be severely disturbed in gastrointestinal milk allergy (31 32, 50, 52) it is therefore not surprising that lactose intolerance should be a common associated finding (34) In this context it should be mentioned that preparations of commercial lactose are derived from cow's milk and have been shown to be contaminated with milk proteins (46)

It has been our experience that symptoms manifested by babies with severe immunological deficiency disorders very closely simulate those manifested by some babies with severe CMA. Both groups of babies have repeated respiratory infections and repeated bouts of diarrhea associated with failure to thrive It is probable that these symptoms are due to the baby's inability to handle bacterial and viral antigens, but it is also possible that they are aggravated by his inability to handle food antigens, and that the absorption of the latter compounds his problems. Such babies may also have disaccharidase deficiencies (11) no doubt secondary to the repeated bouts of gastroenteritis to which they are subject.

SUMMARY

1 A consecutive series of 787 babies born at the University Hospital were followed for 12–36 months in order to determine the prevalence of cow's milk allergy (CMA)

2. Fifty-nine babies (7.5%) were shown by repeated challenge to have evidence of CMA.

3 The main manifestations of CMA were eczema in 27 recurrent diarrhea in 24 recurrent rhinorrhea in 18, repeated vomiting in 12, recurrent bronchitis in 10 and asthma in 7

4 Thirty-four babies had two or more allergic problems, e.g. had recurrent rhinorrhea and eczema or recurrent bronchitis and recurrent diarrhea 25 babies had only one.

5 Babies allergic to cow's milk were often allergic to other foods, 20% for example were allergic to soya.

6. Twenty five babies developed their first symptoms within 7 days of being given their cow's milk formula.

7 Seventeen of the babies lost their sensitivity to cow's milk, 10 of these babies were less than 12 months old. Thirty-eight babies over 12 months of age when last reviewed were still allergic to cow's milk.

8. Babies with CMA, as well as those with other allergic problems, attended their doctors on account of illness more frequently than did the non-allergic babies.

9 Allergic disorders were commonest in the parents and siblings of babies with CMA, and least common in the parents and siblings of the non-allergic children.

APPENDIX A

The stages through which we build up a meat base formula are as follows:

Stage 1

Lamb base (3 cans) 300 g
Dextrose (1/2 cup) 120 g
Distilled water to (48 oz) 1 440 ml
If the above is tolerated, move to Stage 2, and so on.

Stage 2

Lamb base 300 g
Sugar 120 g
Water to 1 440 ml

Stage 3

Add a fat, i.e. corn, safflower or olive oil.
Lamb base 300 g
Sugar 120 g
Corn oil 7.5 ml (2 tsp)
Water to 1 440 ml

Stage 4

Add calcium to bring the calcium content of the formula up to 50 mg%
Calcium chloride 2 g
Calcium lactate 4 g or
Calcium Sandoz Forte 0.75 g (1.5 tablets) in each 1 440 ml.

Stage 5

Add vitamin supplements, e.g. Poly-Vi-Sol 0.6 ml. If the lamb base is not tolerated, substitute other prepared baby meats, e.g. chicken, beef or turkey. If the meats are not tolerated, a supply of breast milk should be obtained. If the corn oil is not tolerated, try another fat, e.g. olive or safflower oil. If the vitamin preparation is not tolerated, place the baby on "Drisdol" Beminal and ascorbic acid. Once a suitable formula has been engineered, keep the baby on this formula until he is gaining weight well. Introducing new foods into his diet should be done reluctantly only one at a time, and no more than one new food a week.

The challenge

When the child has fully recovered he should be challenged with unboiled but pasteurized cow's milk. If he is thought to be exquisitely sensitive to cow's milk, he should be challenged cautiously. He may be offered cow's milk again at a year and if he is still allergic to milk he should be kept off it.

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Department of Pediatrics
University Hospital
Saskatoon, Saskatchewan, Canada

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HEALTH CONTROL OF FOUR-YEAR OLD CHILDREN

AN EPIDEMIOLOGICAL STUDY OF CHILD HEALTH

BY LENNART KÖHLER

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM

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From the Department of Paediatrics, University Hospital, Lund, Sweden

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CONTENTS

This report is a discussion and evaluation of a health control of 4-year-old children

It is based on the following original papers

I Lennart Köhler Physical examination of four year-old children *Acta Paediat Scand* 62 181–192 1973

II Lennart Köhler and Göran Stigmar Vision screening of four year-old children *Acta Paediat Scand* 62 17–27 1973

III Lennart Köhler and Hans-Eric Holst Auditory screening of four year-old children *Acta Paediat Scand*, 61:555–560 1972

IV Lennart Köhler and Kerstin Holst Dental health of four-year-old children *Acta Paediat Scand* 62 1973

V Lennart Köhler and Kerstin Holst Malocclusion and sucking habits of four year-old children *Acta Paediat Scand*, 62 1973

VI Lennart Köhler Hans Fritz and Bengt Scherstén Health control of four-year-old children. A study of bacteriuria *Acta Paediat Scand* 61:289–295 1972

In the text the above papers will be referred to by their roman numerals I–VI

Preventive paediatrics in Sweden is administered by the County Council s Child Health Centres, under the supervision of the National Board of Health and Welfare For a population of approxi mately 800 000 pre school children there are about 1400 Child Health Centres *(Barnavårds-centraler)* in 1966 supervising 600 000 children (2) Two types of Child Health Centres exist. Type I, staffed by a paediatrician and a specially trained children s nurse and Type II staffed by a County Medical Officer and a Public Health Nurse They each serve roughly half of the population of children.

According to regulations, these centres should provide regular health controls of physical mental and social development. They occur 4–7 times during the children s first year of life twice during their second year and later on once a year until school begins at 7 years of age (48) The participation in these health controls is voluntary and free of charge for the parents. Personnel and equipment costs are paid for by the counties. During the infant year the children participate to almost 100%, but as they grow older the attendance rate diminishes rather rapidly and at the age of 4 years, only about half of the children visit the Health Centres (2).

Among medical and social authorities in Swe den, discussions have been held on how to provide more of our pre-school children with preventive care and how to do it efficiently so that more disabling conditions can be detected and treated earlier As it was, many milder chronic disease and minor handicaps were not diagnosed and treated prior to the children s school entry (2).

One way of obtaining an early recognition o handicapping disorders in childhood is to clinically select infants considered to be specially liable t develop handicaps. This risk group of childre

II 1 *Purpose*

The main purpose of this child health investigation was.

1 To study during the pre-school-age the fre quency and types of disabilities and handicaps which may influence the present and future function of the child Special interest was directed to disabilities not previously detected or cared for

2 To develop and test valid and time-saving methods to detect these disabilities.

3 To test an administrative and organizational form for this type of child health study

4 On the basis of our findings, it should be possible to suggest improvements to the ordinary Child Health Services regarding methods, per sonnel and organization

For reasons of availability and convenience children in the city of Lund were chosen as the first population to be studied. One year later children from Dalby a rural district just outside Lund were included.

II.2 *Cooperation with other specialists*

Naturally the discovery of health problems or defects is of no interest whatsoever if there exist no ways or means of treating or alleviating these conditions. Therefore it was very important to plan and perform this investigation in close cooperation with the specialists, inside and outside the hospital, who were to further investigate and treat children referred to them from the health control. A continuous exchange of experience and information was maintained between specialists from the different fields represented in the investi gation (paediatrics, ophthalmology audiology odontology educational psychology public health and administration)

III 3 *Program*

The program designed for the health control included the following items

1 *A thorough physical examination* performed by a paediatrician.

2 *A vision screening* performed by nurses

3 *An auditory screening* performed by nurses

4 *An evaluation of the mental development and social adaptation* performed by a psychologist

5 *A dental examination* performed by a dentist

6 *A laboratory screening* of blood and urine performed by nurses.

II 4 *Personnel and equipment*

The personnel immediately attached to this pro ject consisted of one paediatrician (the author) one psychologist one dentist one registered nurse one children s nurse and one secretary The appointment as registered nurse was held by 3 persons during the study the remaining staff being the same throughout the investigation Before their work started the nurses went through theoretical and practical courses at the Depart ments of Ophthalmology and Audiology learning how to perform screening of vision and hearing. Since the success of accomplishing these screening examinations basically depends on the screener s ability to establish a warm and confident contact with the children nurses with training and exper ience of children should make the best exami ners. The time and skills of ophthalmologists, orthoptists and audiometrists should be reserved for diagnosing and treating children referred to them by means of the screening program.

A child Health Centre with ample space was available in Lund as premises for the study Great effort was spent in making the surroundings look different from those of a hospital ordinary living-room furniture was used whenever possible and textiles and walls had warm, gay colours. In Dalby the ordinary office of the district nurse was used. For economical and practical reasons the dental examination took place at the Department of Public Dental Health. The personnel wore their own clothes, no white coats being allowed except for the dentist, who needed them as protection. The possibilities for carrying out a health control of this kind depends to a great extent on the children s cooperation, and as it could be anticipa ted that many children had memories of painful visits to doctors, it seemed reasonable not to remind them too obviously of these consultations.

II.5 *A nation-wide health control of 4-year-old children*

Shortly after the planning of our project was started the Minister for Social Affairs instituted an analysis of Child Health Care in Sweden and, subsequently the National Board of Health and Welfare worked out a program for a general health control of all 4-year-old children in the country to be started in 1969 (2). The purpose of this health control was to bridge the gap of efficient health care between infancy and school age i.e. partly the same as in our investigation, and the program was similar. Our project was adopted as a pilot study and supported by grants from the Ministry. A preliminary report from the first part of our study was published in 1969 (76). Also other pilot studies, although differently designed and organized were started later on. Hitherto short descriptive results have been presented from Uppsala (74), and Göteborg (5).

III POPULATION

III.1 *General description of the area and the population*

Lund and Dalby are situated in southern Sweden (see map Fig 1). Lund is a city of about 50 000 inhabitants, a centre of education medical care and administration, dominated by the university (20 000 students) and large university and county hospitals.

Dalby in this context means the communities of *Dalby Genarp and Veberod with a population* of about 8 500. Parts of it are still mainly farming areas, while other parts have expanded rapidly during the last decade and become increasingly like a suburb. The differences in the main industry among the population of Lund Dalby and the whole country are evident from Table 1.

Table 1 *Relative distribution of main industry among economically active population of Lund, Dalby and the whole country*

Population and housing census 1965

Main industry	Lund (%)	Dalby (%)	Whole country (%)
Agriculture et	2	26	10
Manufacturing and construction	31	40	44
Trade and communication	18	20	23
Public service	49	14	23
	100	100	100

The influence of the social environment upon growth and development, health and disease has been confirmed in many studies and is now common knowledge. Therefore in a study of child health it is necessary to include some kind of description of the way of life of the children and their families. Usually some more or less elaborate stratification of the population into social or economic groups is practised. In Sweden, the classification into 3 socio-economic classes or

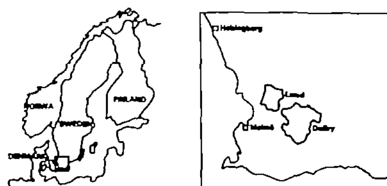


Fig 1 Map of Scandinavia, showing the areas studied.

groups has been widespread (I upper class II middle class, III working class) (16) although the method has been heavily criticized as being inadequate unreliable and unfair and not suitable in our modern society (25). A new classification into 11 occupational groups is proposed partly based on an international system (25)

However in a relatively small survey of this kind it is only possible to use a few groups. Therefore although well aware of its limitations we chose to revive once again the old 3-graded socio-economic classification system, which pays attention to the occupation and indirectly to the education and economy of the head of the family usually the father The mother s occupation is not usually reflected in this classification, but in some comparisons within our study where the mother s role was considered especially important her education was used as a parameter (e.g. principles of upbringing, oral hygiene). Of course when the mother is single the socio-economic classification is based on her occupation

It must be emphasized that class distinction in Sweden is not very pronounced (42) The excellent economic situation of the country combined with strong political goals including extensive social welfare have brought about a far-reaching social equality (63)

To all intents and purposes the lowest class, corresponding to many foreign classifications has been eliminated, and with it the disadvantages and opprobrium attached to such a designation (42)

The distribution of the parents of our 4-year-old children on the socio-economic groups are shown in Table 2 as well as the percentage of parents with academic education Although the figures from Lund and Dalby in Tables 1 and 2 are not altogether comparable with those from the whole country they give nevertheless a rough idea of the situation Since these very important background variables show such a great disparity from the conditions in the whole country it is also probable that the results from this limited survey cannot be regarded as altogether valid for the whole country

III.2. *Selection of children*

The county population register sto ed on magnetic tapes and up-dated every week was used to select children aged 4 years nd li ing permanently in Lund and Dalby Thus every child on the official register was included even though temporarily absent. Children living temporarily in the areas but registered elsewhere were excluded Information on children moving into the areas during their 4th year of life was collected continuously and these children were included in the study Correspondingly children moving out of the areas before their 4th birthday were excluded

Table 2. *Relative distribution of socio-economic groups and academic education among families of 4-year-old children in Lund and Dalby and among the population of the whole country*

	Parents of 4-year-old children in		Population of the whole country
	Lund (%)	Dalby (%)	(%)
Socio-economic group			
I	31 7	9.3	10.5
II	35 4	39.6	52.1
III	32.9	51 1	37 4
	100.0	*100.0*	*100.0*[a]
Academic education of parents			
husband only	16.9	4.5	3 2
wife only	2.9	1 1	0.2
both	19 1	1.1	0.7
total	*38.9*	*6.7*	*4.1*[b]

[a] Refers t a sample f the country s households with children aged 2–6 years (67).

[b] Refers to households with children under 7 years of age (8).

III.3 *Participation in the study*

The population of 4-year-old children born 1963–1965 and living in Lund and Dalby during 1967–1969 as well as their participation in the main study is shown in Table 3 The difference in the attendance rate between Lund and Dalby was not significant ($p>0.05$) Slightly more boys than girls participated ($p<0.05$).

For economic and practical reasons the study of bacteriuria was limited to children born in 1963–1964 and the main dental study to children in Lund born 1963–1964 and in Dalby to children born in 1964–1965 (see Papers IV V and VI)

Table 3 *Population of 4-year-old children and their participation in the health control*

	Invited children			Participating children					
	Boys	Girls	Total	Boys		Girls		Total	
				n	%	n	%	n	%
Living in Lund	1 183	1 113	2 296	1 136	96.0	1 043	93 7	2 179	94.9
Living in Dalby	141	136	277	136	96.5	132	97 1	268	96.8
T tal	1 324	1 249	2 573	1 272	96 1	1 175	94 1	2 447	95 1

The participation in our study was indeed very high, 2447 out of 2573 or 95 1% It proves that one of our aims was achieved, i.e to construct and carry out a health service that was convenient and accessible for parents and children and also recognized by the parents as being important for their children s health. Of course there were several factors which facilitated the performance of our health control Firstly Sweden has a long history of efficient population statistics, dating back to 1749 and claimed to be the oldest in the world. Today the registers are even more reliable up-to-date and easily accessible by the use of computers. Secondly the study was performed in a limited, densely populated area with small distances and no communication problem.

Thirdly it is unquestionable that the population in these areas is unusually well equipped and prepared to fill in questionnaires to be interviewed and to participate in examinations of different kinds, partly because a large proportion of the inhabitants have an academic education and partly because people are used to scientific investigations from various university institutions. Fourthly the support of the project among the authorities and specialists was so positive that we were allowed to plan and perform the study under optimal conditions as regards personnel equipment premises, and use of hospital facilities for the follow-up of referred children.

III 4 *Non-attendance*

In spite of every effort to obtain a full cooperation the problems of non-attendance are unavoidable in a health control of this kind. It is often argued that those not wishing to cooperate are non-representative of the total group in many respects (27 57). It would therefore be interesting to study their background health and reasons for noncooperation.

III 4 1 *Medical care.* For the 126 children who did not participate in the study records from the Child Health Centres from the Children s Hospital (in- and out-patient wards) from the Eye Clinic from the Audiology Clinic and from the Surgical and Orthopaedic Clinics were scrutinized. Altogether 15 children were under current professional care due to handicapping disorders (Table 4) Ten of these children were taken care of by mainly one clinic and 5 by 2 clinics. Their handicaps are mentioned in papers I, II and III It may be assumed that their parents had a valid excuse for not participating in a health control

Out of the remaining 111 children information could be collected on 84 from the various medical records. Generally the visits to the Child Health Centres were infrequent and during the last year only 18.8% had visited a Child Health Centre compared with 41.3% of the participating children.

In general, the appointments at the Children s Hospital concerned minor ailments such as infections, rash and eczema

It seems unlikely however that major physical handicaps would have been overlooked at these visits, although it is quite conceivable that some deviations, not easily detected without proper examination may hide among these children, e.g.

Table 4 *Non-attendant children under professional care for handicapping disorders*

Clinic	Number of children		
	Boys	Girls	Total
Children Hospital	5	5	10
Eye Clinic	2	5	7
Audiology Clinic	1	2	3
Total number of children under professional care	6	9	15

vision and hearing defects bacteriuria, caries, social understimulation and intellectual subnormality Actually at the compulsory health control in school at the age of 7 years 2 out of these 84 children have already been found to have deep amblyopia and 1 to have bacteriuria

No information was available from any records for 27 of the children.

III 4.2 *Reasons for non-participation.* The reasons for the non-participation of the 111 children not under care for handicapping conditions were investigated by trained interviewers who visited the parents in their homes. Parents of 85 children were traced and interviewed As can be seen in Table 5

Table 5 *Reasons for non-attendance. Interview of parents of 85 children*

Several reasons may be given

Reasons	Number of children n	%
No time	38	44 7
Child ill	8	9 4
Parents negative to health controls	16	18.8
Children negative to examinations	8	9 4
Regularly health controlled by other doctors	12	14 1
Other reasons	27	31.8

the reasons given could be roughly divided into 3 parts those who were unable to attend those who refused to attend and those who were already attended to These reasons are the same as those reported from health controls of adults (68) From the children s and also from our point of view these parental explanations are not satisfying, since non of them can exclude disabilities in the children.

Table 6. *Some socio-economic variables among participants and non-participants*

	Participants (%)	Non-participants (%)
Socio-economic group		
I	32.1	31.0
II	34.4	24.6
III	33.5	44 4
Academic education of father or mother	35 4	25 4
Dwelling		
modern	90.4	76.5
semi-modern	6.1	11 8
un-modern	2.1	8.2
Single parent	8.4	11.9

III 4.3 *Social background.* It is often said that hard to-reach families belong to lower socio-economic groups (14 49) and that the families need for advice and support is greater than that of other families (2) To test this hypothesis a comparison was made between the participants and the non-participants regarding some available socio-economic factors As shown in Table 6 non-participating families seem to have a somewhat poorer socio-economic background the difference in socio-economic groups and academic education being significant at the 5% level in standard of dwelling at the 0 1 % level No difference was found regarding "incomplete" families ($p>0\ 05$)

Another method of judging the families social wellbeing is to consider their need for social assistance reflected by Public assistance received *(Socialbidrag)* attention by the Child Welfare Committee *(Barnavårdsnämnd)* or the Temperance Board *(Nykterhetsnämnd).* The social registers were scrutinized in these respects and the findings for our non-attendant families were compared with those of a control group For each of the 126 non attendants a child of the same sex and

Table 7 *Need for social assistance in 126 non-attendant families and 126 control families*

Type of social assistance	Non-attendant families n	%	Control families n	%
Public assistance	22	17.5	9	7 1
Attention by Child Welfare Committee	19	15 1	6	4.8
Attention by Temperance Board	4	3.2	1	0.8
Total number of families with social assistance	34	27 0	14	11 1

socio-economic group born on the same day or on one of the immediate following days, was selected among the participants and constituted the control group

The result of this comparison is shown in Table 7 27.0% of the families of the non-attendant children were found in the social registers as compared with 11 1% of the control group The difference is significant at the 1% level

Thus, the hypothesis was proved to be correct the non-attendant families had less education a more burdened social situation and they provided less health care for their children. Although the participation in this epidemiological study of child health was very high it is strongly desirable with regard to health services that these hard-to-reach families are also included and surveilled in a Child Health Program. Therefore even greater efforts must be made to reach the whole child population by making the service more meaningful convenient and available and by administering it so as to protect the time money and dignity of the recipients (49). Offering favourable conditions is however not always sufficient It is often necessary to personally get in touch with these parents and explain to them the purpose and the benefits of the investigation.

IV PRACTICAL PERFORMANCE OF THE HEALTH CONTROL

IV 1 *Invitation*

Shortly before their 4th birthday the children were invited to participate in the health control by a letter to their parents. The invitation described the purpose of the investigation and the different items included and presented the investigators by name and title It also reassured the parents that all information about the family would be treated confidentially and that detected deviations would be cared for after full discussion with the parents. Finally a date and a time was suggested for the first appointment. The invitation was accompanied by a questionnaire to be delivered filled in at the first visit to the Child Health Centre If the appointment was not kept the parents were reminded several times, first by mail and then by telephone Sometimes a personal call to their homes was made

IV 2 *Examinations*

Since the health control was designed to be comprehensive and included several time-consuming items it was divided into 3 parts It meant that the children and the parents had to attend on 3 separate occasions On the other hand, a child of 4 years could hardly be expected to cooperate fully during 2–3 hours of examination. At the first visit the screening of vision and hearing and the physical examination including laboratory examinations, were performed. Since a major problem both in vision and hearing screening is one of cooperation i e to catch and keep the children's attention, the examinations were performed in rapid succession in the same room and by the same examiner Usually 15 min was enough for the two screening procedures When the child failed the screening at the first trial a new test was performed on a later occasion. After a second failure the children were referred for further examination to the ophthalmologist or the audiologist.

After a short rest in the waiting-room, the physical examination which took 20 min was carried out. All findings were discussed with the accompanying parent, and advice and treatment for minor medical problems were offered. Children with health problems considered to be functionally important at the present or in the future and not under current professional care were referred for further evaluation and treatment to the respective departments of the University Hospital of Lund.

At a second visit, the evaluation of the mental development and social adaptation was performed by the psychologist. The children were observed and examined in groups of 4–5 according to a standardized scheme Afterwards, each mother was interviewed separately the questionnaire scrutinized, and problems of behaviour and development were discussed Advice was always given,

sometimes psychological and educational treatment was also instituted When necessary the child was referred for further psychological medical and social evaluation and treatment A part-report on the psychological investigations, purpose methods, results and follow-up is given elsewhere (32–34).

The dental examination was carried out at a third visit at the Department of Public Dental Health. The examination itself took an average of 20 min and was followed by a 30 min discussion with the mother regarding the child's eating and sucking habits oral hygiene and earlier dental care. In Dalby where medical and dental facilities are situated in the same building, visits 2 and 3 were performed successively on the same day Children with caries and need for orthodontic care were referred for treatment.

IV.3 *Registration of data*

Standardized forms for the various examinations and for referral were constructed When the record was completed and the examination finished, data from the questionnaire and examination forms were transferred to punched cards and stored on magnetic tapes. No printouts were made by the computer but the original record was kept at the Child Health Centre Statistical computation of the material was later performed at the Computer Centre of Lund University (Univac 1108) using general computer program (69) as well as specialized programs designed for this investigation. Minor statistical analyses (chi-square tests for normal distribution) were performed on a desk computer (Olivetti Programa 101)

V THE METHODS OF EXAMINATION AND THEIR APPLICABILITY IN THE STUDY

The traditional way of providing health care for children is to offer periodical medical evaluation These evaluations consist mostly of history-taking and examinations, and are usually performed by specialists mainly physicians Lately other approaches to identify health problems have been introduced into the Child Health Services e.g screening by tests by examination, by observation and by interview performed by non-physician personnel (15) and using questionnaires completed by parents or teachers (49)

In this study traditional medical evaluation (physical examination Paper I and dental examination, Papers IV and V) was used as well as screening by specific tests (vision examination, Paper II auditory examination Paper III examination of bacteriuria Paper VI) screening by examination (neurological examination Paper I) screening by observation (psychological examination (33) screening by interview (psychological examination (33) and dental examination Papers IV and V and a parental questionnaire

In addition records from the Children's Hospital from the Eye Clinic and from the Audiology Clinic were scrutinized to identify children with previously known important physical disorders Unfortunately records from the Surgical and Orthopaedic clinics could not be checked, as they are filed according to day of birth not year of birth. However children with serious surgical or orthopaedic disorders are almost invariably also investigated by paediatricians, and therefore these children should be found in the files of the Children's Hospital

Although there are a few private paediatricians, ophthalmologists and otologists in the area, our experience is that it is highly improbable that the facilities and resources of the University Hospital are not used for assessing and treating children with handicapping disorders Thus records of children who are controlled and treated mainly by private doctors should also be found at the hospital

V.1 *Questionnaire*

Some information on the children's health development previous and present adaptation problems and the family's social standard was desirable to serve both as anamnesis before the medical and psychological examinations, and as an

instrument for identifying children at high risk of having health problems

Familiarity with the ordinary records kept at the Child Health Centres convinced us that they were highly unsuitable for these purposes their information is unstandardized, incomplete and sometimes inadequate Furthermore for a great part of the children, these records do not cover more than the first years of their lives. Therefore other sources and methods must be used Much useful information about the children and their families can be found in records from the hospitals in- and outpatient wards from private doctors from social registers but it was considered too time-consuming, expensive and inconvenient to collect all these widely scattered data

A questionnaire i.e. a self administered medical history taking, has several advantages (45)

1 All patients are asked the same questions, formulated in the same manner

2. The questions are answered at home i.e. in a familiar and unstressed surrounding.

3 Much time is saved for the physician and the nurse in the collecting of data.

4 The information may easily be coded and stored in a computer facilitating retrieval of data.

5 The influence of the examiner is reduced or eliminated, as compared with the dialogue method.

By a follow-up of the answers in the questionnaire with further questions, some of the disadvantages with this method were removed completion of omitted answers could be made and fuller information on specific points could be gathered and, also the benefit of a personal contact with the parents was enjoyed

All retrospective collection of data gives a certain unreliability to statements of events that took place a long time before the investigation (6 13 41 72).

However for our purposes a questionnaire to the parents was considered the most suitable way of collecting basic information about the child and its family The questions were mostly of the fixed choice type i.e "yes no or a multiple choice list although ample space was left for narrative comments Completion of omitted answers was made when possible during the medical examination. An evaluation regarding reliability and validity of the psychological and educational part of the questionnaire was made in an intensive pilot study of a sample of the material (33). Both reliability and internal and external validity were found to be adequate for the purposes of the study

Although the questionnaire was a lengthy one the parents tried hard to answer all the questions.

By computing information from the questionnaires regarding symptoms and signs previous and present health birth complications, and heredity with actual findings of physical disorders it was possible to designate certain children as being at risk of having, e.g vision and hearing disturbances, bacteruria or neurological deviations (see Papers I II III and VI)

However the ability of this parental information to identify children, who by other methods of examination were found to have physical disorders, was very low i.e. the relative sensitivity (see page 16) of the questionnaire was inadequate Hence the questionnaire was not suitable as a screening instrument

V.2. *Physical examination*

Since no specific screening tests are available to detect physical health problems or handicaps at this age (10) other procedures were applied ordinary clinical evaluation by examination and by observation The methods are well-known and used in every-day practice by all paediatricians. The examination was rather detailed and was performed carefully and thoroughly The procedures – examinations, observations and registrations – followed a strictly standardized scheme

In order to diagnose and treat a sick child a physical examination can always be performed also against the child's will However a health control carried out to detect even minor deviations of health and function must rely to a great extent on the child's cooperation Therefore great effort was spent in attracting and keeping the children's interest throughout the examination by including items which were fun for the children at the same time as they gave valuable information to the examiner Examples of such items were pouring water into cups, running, hopping on one leg, cutting with a pair of scissors playing with beads. Procedures least likely to disturb the child were carried out first such as looking at the hands, and noting the active power in the arms while procedures which might excite or frighten were post

poned to the end e.g. measuring the blood pressure and the hæmoglobin concentration In this way full cooperation was reached in 99.5% of all children In the few uncooperative children at least some of the motor functions could be studied as they struggled to get out of the room!

V.3 *Vision screening*

One of the reasons for postponing this health control to the age of 4 years was that this age was presumed to be the earliest one at which specific mass screening tests involving a great deal of cooperation (e.g. testing of vision) could be used on the majority of the children.

Many tests have been used and recommended for pre-school vision screening although only few of them have been critically evaluated regarding both overreferral and underreferral. The Marquez Boström s hooks, widely used in Sweden is one of them. In order to detect strabismic children with normal visual acuity a cover test and a test of the binocular function (Stereo-fly test) were also included The tests were easy and quick to carry out and a complete examination could be performed on 98% of the children.

The usual way of evaluating a screening test is to calculate the sensitivity and the specificity The use of these conceptions, however requires that a diagnosis is established or ruled out for every person tested by the screening procedure regardless of whether the person screened negative or positive (70). This type of evaluation was made in our study of bacteriuria (Paper VI). For economic reasons it was not possible to offer each child a full ophthalmological examination and instead we tried to evaluate the screening methods by using control groups and by rescreening the children when they began school at 7 years of age So far results from the school-screening are only a ailable for some of our children but the follow-up continues

The ontrol groups and the follow-up at school showed that few children needing ophthalmological treatment were missed and m st important that no children with functional amblyopia or strabismus passed the screening tests

For purposes of comparison between the 3 screening tests, the relative sensitivity and specificity may be calculated assuming that children negative to all of the tests are truly free from eye disorders (70). In that way the relative sensitivity of the visual acuity test was 97.0%, the fly test 11 7% and the cover test 7 4% while corresponding figures for the relative specificity were 97 4% 99 6% and 99 8% (Table 8).

It was also found that the adapted screening level of 5/6 was appropriate A lowering of the passing standard to 5/10 would reduce the overreferral from 15.5% (53 out of 343 referred for failing the 5/6 level) to 7 7% (13 out of 168 failing the 5/10 level) but at the same time 25.5% (38/149) of all children needing treatment would then have been overlooked (Paper II Table 4) In other words, the relative specificity would increase

Table 8. *Relative sensitivity and specificity of 4 different screening procedures to detect eye disorders*

	Diagnosis		
Screening test result	Eye disorder	No eye disorder	Total
1 Visual acuity test, screening level 5/6			
Positive	290	53	343
Negative	9	1972	1981
Total	299	2025	23 4[a]
Relative sensitivity = $\frac{290}{299}$ x 100 = 97 0 %.			
Relative specificity $\frac{1972}{2025}$ x 100 97 4 %.			
2. Visual acuity test, screening level 5/10.			
Positive	155	13	168
Negative	144	2012	2156
Total	299	2025	2324[a]
Relative sensitivity 51 8 %.			
Relative specificity 99 4 %.			
3. Wirt Fly Stereo test			
Positive	35	9	44
Negative	264	2016	2180
Total	299	2025	2324[a]
Relative sensitivity = 11 7 %.			
Relative specificity 99 6 %.			
4 Cover test			
Positive	22	4	26
Negative	277	2021	2298
Total	299	2025	2324[a]
Relative sensitivity 7 4 %			
Relative specificity 99 8 %.			

[a] 67 children under professional care are excluded.

to 99.4% but the relative sensitivity would decrease to 51.8% (Table 8). Such a modification of the visual acuity test could therefore not be accepted.

Thus it could be concluded that the present visual acuity test is accurate enough as a screening method for eye disorders in pre school children. Both the cover test and the fly test are too unreliable to be used as the only methods. In an ambitious program however they may be used as a complement to the visual acuity test

V 4 *Auditory screening*

In general the ordinary mass screening methods to detect hearing defects cannot be carried out until the child is past the age at which special treatment of these defects should begin (15)

More refined screening techniques, useful for even newborn infants have been designed but are not commonly used or even recommended as routine methods (12) Lately a new "contact" test to screen for the infant s ability to hear and to listen, has been constructed and tested on a small scale (3 29) Until the results of this and other methods have been confirmed in more extensive studies and follow-ups we must rely on skilled as well as unskilled observation in order to detect hearing impairment in small children.

The pure-tone audiometry is well suited for the screening of somewhat older pre school children especially if the play-audiometry principle is used, as in this study The method was easy to learn for the nurses, the examination took 8 min on average and could be performed on 98 9% of the children.

The sound intensity used as the passing level for the test was 20 dB ISO except at 250 cps, where 25 dB was accepted because of the unavoidable environmental noise in the testing room. Similar procedures have been applied in other investigations (4 40). During the first year only 3 frequencies were used at testing, during the following two years, 6 frequencies. Calculations from the results of the last two years of examination show that the relative sensitivity of detecting hearing impairments of any origin is 70.5% and the relative specificity 99.5% when testing at 250 1000 and 4000 cps. Corresponding figures for testing at 250 4000 and 8000 cps are 97 4% and 98 6% respectively (Paper III Table 3)

Since the screening method is quick and easy to carry out, there is no reason for reducing the efficiency of the test by limiting the number of frequencies used

Retesting children who fail at the first screening before referring them to an audiologist, and treating them with nasal decongestants between the two tests, seem to be a wise procedure In this way the number of overreferred children is reduced to an acceptable point (1 2% of all tested) and the burden on the audiologist is lightened The professional examination of our control group showed that it is unlikely that many children with important hearing loss were missed at the screening.

V.5 *Dental examination*

No specific screening test is available for detecting dental disorders. In the clinical examination of caries, gingivitis and malocclusion certain sources of observational error are inherent, of both systematic and accidental type However in this study several steps were taken to reduce such errors.

1 The same dentist, with long clinical experience performed all examinations.

2. Diagnostic criteria were standardized and the dentist was well acquainted with these criteria from a training period spent together with a paedodontist and an orthodontist until they were in agreement on their judgment.

3 Methods of recording were also standardized using specially constructed dental charts for the examination and for the interview

4 Two equivalent sets of room, equipment and instrumental set up were used during the study one in Lund and one in Dalby

5 Ample time was allowed for the examination of each child.

Since an unselected population of pre-school children was examined with these precautions it seems justified to compare the oral health in different subgroups of the material (e.g. sex, area of residence and socio-economic groups).

V.6 *Urinary screening*

Examination of the urine is an old and widely used procedure to detect diseases in adults and children

In pre-school children as well as in schoolchildren the traditional examinations – in popula

Table 9 *Number of functionally important health problems according to diagnoses*

	Among 2 447 examined children		Among 126 non-participating children		Sum	
	n	%	n	%	n	%
Neurological	67	2.7	6	4.8	73	2.8
Other somatic	68	2.8	4	3.2	72	2.8
Cardiac	15	0.6	1	0.8	16	0.6
Other pediatric	16	0.7	3	2.4	19	0.7
Surgical	27	1 1	0	0	27	1 1
Orthopaedic	10	0.4	0	0	10	0.4
Dental	204	8.3	–	–	204	7.9
Visual	221	9 0	7	5.5	228	8.9
Auditory	41	1 7	3	2.4	44	1 7
Bact riuria	9	0.4	–	–	9	0 4
Total	610	24 9	20	15 9	630	24.5

In the *dental study* children designated as "emergency cases" were counted as having functionally important health problems, 194 children in the main study group and 10 children in the experimental group (Paper IV Table 2 and page 6) Malocclusion was not considered to be a functionally important health problem at this age

The ophthalmological findings in children referred for *visual disturbances* were evaluated in terms of need for professional care and groups 2–3 were designated as "significant eye disorders" (Paper II page 18) i.e an early treatment would be advantageous for the visual prognosis These 154 children (Paper II Table 2) were considered as having functionally important health problems as well as the 74 children with previously known and treated eye disorders (Paper II page 21)

Most of the newly detected *hearing impairments* were due to conductive hypoacusis. 36 children with severe middle ear infection and 2 with compact cerumen as well as the one with a more serious sensorineural hearing loss (Paper III, Table 1 and page 556) were included in the group of children with functionally important health problems as were 5 children receiving special education due to serious sensorineural hearing loss

The finding of *bacteriuria* in 9 girls was considered important because of the possible connection with renal disease later in life (Paper VI page 289) The presence of non-persistent proteinuria was not regarded as important

The mild *anaemia* in 20 children (Paper I Table 8) was not considered to be functionally important, since the haemoglobin concentration was not very low and since the children s general health did not seem to be impaired.

The number of functionally important health problems thus defined in the total population of 4-year-old children is summarized in Table 9

The concept of health problem and in particular of functionally important health problem is not easily defined or demarcated Some of our demarcations are rather arbitrarily made and other investigators with different backgrounds and training, or working under other conditions could easily find other angles of approach and question our conclusions. For instance we think that a child at risk of developing amblyopia of one eye has a functionally important health problem. Why is it so important to have full or nearly full sight in both eyes? It is true that he may not qualify for some professions where a perfect stereoscopic vision is necessary e.g. artillery-officer but he is not handicapped in his daily life since his visual acuity equals that of the better eye It is moreover true that he may contract a disease or injure the healthy eye and therby be handicapped. Although no figures seem to be available on this specific problem, the risk cannot be too great. Nevertheless we think that it is important that children should have optimal use of their main information medium, and that a suboptimal function, be it a functional amblyopia or a significant anisometropia, may limit or distort their true conception of the surroundings and cause unnecessary strain.

Such reasoning may be valid in an affluent society where life threatening epidemics and nutritional deficiencies are eradicated. In other countries

these more subtle views on optimal health should rightly be regarded as a waste of time energy and money

The same arguments can be applied to the concept of minimal brain dysfunction which, furthermore is a highly controversial subject. Objections have been raised to the assumption that a specific syndrome of hyperactivity impulsivity and clumsiness, caused by organic brain damage exist at all (19 20 54 58). This condition may instead be associated with any degree of psychiatric neurological or intellectual impairment (20 22). Whatever these children are called they constitute problems for themselves and their surroundings, at the present and in the future By recognition and treatment, better prospects for their adjustment and function are reached (11 73).

On the other hand, children with gross cerebral palsy severe hearing loss, or muscular dystrophia can hardly be disputed as having functionally important health problems

This implies that widely differing disorders are included in the concept of functionally important health problems with varying impact on the children's health and development The justification for collecting all these disabilities under one heading is that we believe that they are all in some way or other important for the child and that we have the resources for detecting and taking care of them.

Table 10 *Functionally important health problems found in 2 447 four-year-old children*

	Number of children		Number of health problems	
	n	%	n	%
Previously known and treated important health problem	132	5.4	172	7.0
Newly detected important health problems	437	17.9	507	20.7
Sum of present important health problems	529	21.6	610	24.9

VI.2 *Previously known and newly detected health problems*

Table 10 shows the number and percentage of children with important health problems divided into previously known and newly detected as well as the number and percentage of important health problems found in these children.

Furthermore among the 126 children who did not participate in the study 15 children had 20 important health problems (Table 9) a figure which slightly augments the percentage of previously known health problems but not that of the sum of present health problems

Thus, based on these concepts of health prob-

Table 11 *Associations of functionally important health problems among 529 4-year-old children*

	Children with functionally important health problems													
	Neurological		Other somatic		Dental		Visual		Auditory		Bacteriuria		Total	
Children with	n	%		%		%		%		%		%		%
One or more health problems	67	–	68	–	204	–	221	–	41	–	9	–	529	–
One health problem only	44	65.7	43	63.2	164	80.4	175	79.2	31	75.6	8	88.9	465	87.9
Two or more health problems	23	34.3	25	36.8	40	19.6	46	20.8	10	24.4	1	11.1	64	12.1
Combinations														
+ Neurological	–	–	1	1.5	9	4.4	16	7.2	1	2.4	0	0	23	4.3
Other somatic	1	1.5		–	11	5.4	10	4.5	4	9.8	0	0	25	4.7
+ Dental	9	13.4	11	16.2	–		19	8.6	4	9.8	1	11.1	40	7.6
Visual	16	23.9	10	14.7	19	9.3	–	–	6	14.6	0	0	46	8.7
Auditory	1	1.5	4	5.9	4	2.0	6	2.7		–	0	0	10	1.9
+ Bacteriuria	0	0	0	0	1	0.5	0	0	0	0	–	–	1	0.2

Within each column, the same child may be found in more than one of the combinations, and thus, the column sum of the combinations may be higher than "1 or more health problems"

lems It is calculated that the gross prevalence of functionally important physical health problems in this total population of preschool children was just under 25%, found in 21.6% of the children. Out of these health deviations 28.2% were previously known and cared for If the dental findings are excluded the prevalence of health problems will be 16 6%, found in 15% of the children, 42 4% being previously known.

VI.3 *Characteristics of the functionally important health problems*

It is evident from Table 10 that a certain overlapping between health problems exist and Table 11 shows the health problems which tend to be associated with each other To avoid too small groups cardiac, orthopaedic, surgical and other paediatric health problems are put together as "other somatic health problems"

Most of the children 87 9% had only one important health problem. Only one strong association was found among the health problems significant eye disorders were found more frequently among children with neurological disorders than among children with other disorders or among healthy children This association is highly significant ($p < 0.001$) and depends on the well-known connection between strabismus and neurological disorders (1 71). since neurological deviations were not significantly more frequent among children with eye disorders *without* strabismus than among healthy children (4.5% and 2.3% respectively $p < 0.05$). Thus children with strabismus could be regarded as being at risk of also having neurological disorders, and vice versa.

Furthermore children with "other somatic problems" seemed to be at risk of having other types of health problems too This association was found in 36.8 % ($p < 0.01$) mostly regarding dental deviations (in 16.2 $p < 0.05$) and auditory impairment (in 5.9 %, $p < 0.05$)

VI 4 *Characteristics of the children*

In Table 12 children with present important health problems are compared with the rest of the studied child population with respect to sex residential area (urban or rural) and socio-economic group These background factors varied considerably according to diagnoses. Slightly more boys than girls were affected with important health problems although this difference was statistically significant only with regard to neurological deviations. Most other studies of chronic illness in childhood show a preponderance of boys over girls, especially regarding motor disturbances (14 53 59 76).

The finding of more health problems in the rural area (Dalby) than in the urban area (Lund) was consistent throughout the various groups of diagnosis (except "bacteriuria") and statistically significant regarding "dental" "other somatic" and "total" health problems If the dental findings

Table 12 *Percentages of children with functionally important health problems distributed on sex area of residence and socio-economic group. Comparison is made with the distribution of children without functionally important health problems*

	Background factors									
	Sex			Area of residence			Socio-economic groups			
Health problems	Boys	Girls	Difference	Lund	Dalby	Difference	I	II	III	Difference
Neurological	3 9	1 4		2.6	3.7	NS	2.0	2.4	3.8	NS
Other somatic	3 2	2 2	NS	2.5	4 9		2 0	3 0	3.2	NS
Dental	7 9	8 8	NS	6.8	20.5	**	0.9	7.3	16.6	***
Visual	8 3	10 3	NS	8.9	11 7	NS	8 0	7 4	12.3	
Auditory	1 7	1 7	NS	1 6	2.3	NS	1 7	1.4	2.0	NS
Bacteriuria (only girl)	–	0 9	–	0.9	0	NS	0.3	1.2	0.8	NS
Sum previously known	5 5	5 1	NS	5.2	6 7	NS	4.2	5.0	7.0	
Sum newly detected	17 7	17 9	NS	15 9	19 4	NS	9.8	16.2	27 1	**
Total health problem	21 8	1 4	NS	19 9	35 8		13 5	19 7	31 4	**

NS not significant $p < 0.05$ $p < 0.01$ $p < 0.001$

are excluded the difference of total health problems between the two areas will be significant only at the 5% level (19 4% and 14.5% respectively)

In Lund the regular health surveillance of infants and children is performed by paediatricians and registered children's nurses i.e. by Child Health Centres of type I while the children in Dalby are surveilled by district doctors and district nurses, i.e. by Child Health Centres of type II (see page 7) It was found that the attendance to the ordinary Child Health Centres during the year before this health control was about the same in Lund as in Dalby (41 9 % and 36.6 % respectively $p>0.05$)

Since examination of vision hearing bacteriuria and teeth was not included in the ordinary health surveillance of smaller children neither in Lund nor in Dalby a comparison was made between the two areas regarding "neurological" and "other somatic" health problems which could be expected to be detected and referred for treatment at the routine medical examinations The comparison is showed in Table 13 It is found that the frequency of both previously known and newly detected health problems of this kind is greater in Dalby than in Lund, although the difference is statistically significant only regarding the sum (5 1 % and 9 0 % respectively $p<0.05$) The interpretation of these figures is that the differences in prevalence are not due to differences in the skills or attention of doctors and nurses at the Child Health Centres but rather to the different structures in the population in Lund and in Dalby The higher the socio-economic group the parents belonged to the less frequently did their children have important health problems (Table 12), and families in Lund more frequently belonged to higher socio-economic groups than families in Dalby or in the country as a whole (see Table 2). The distribution of these health problems on the socio-economic groups did not differ significantly between Lund and Dalby ($p>0.05$)

The dental findings were most responsible for the different prevalence of health problems in the socio-economic groups. If these findings are excluded the prevalence of total health problems will be more equally distributed and the differences not statistically significant (12.5 % 13 4 % and 18.9 %, respectively $p>0.05$)

The significance of social conditions for child health development has been demonstrated in several investigations (For review see 76). Moreover in a recent sociological study of adult health in Sweden a similar inequality in health problems was found between the three socio-economic groups (28).

Table 13 *Distribution of neurological and other somatic health problems in 2 179 children in Lund and 268 children in Dalby*

"Neurological" and other somatic *health problems*	Lund		Dalby		Difference	Sum	
	n	%		%			%
Previously known	56	2.6	12	4.5	NS	68	2.8
Newly detected	55	2.5	12	4.5	NS	67	2.7
Total	111	5 1	24	9 0		135	5.5

VI.5 *Comparisons with other studies*

Comparisons with other epidemiological studies on child health are difficult, often impossible due to *substantial differences in populations, definitions* and methods

Nevertheless Pless & Douglas (53) in summarizing several epidemiological studies of child health, state that there seem to be a general agreement that the total prevalence of chronic conditions in most populations under 20 lies between 10 and 15 %. Our results of 15 % of the children with functionally important health problems support this view However if the dental findings are included as is hardly ever done in other studies, the figure is instead 21.6 %. Furthermore phychological and educational health problems are not included in this part of the report, and they will undoubtedly increase the number of affected children.

Reports, although less detailed from two smaller and differently designed Swedish studies on 4-year-old children have been published (5 74) Both found few serious somatic deviations that were not known before Visual and auditory disturbances were rather common. One of the studies (5) found a prevalence of caries and malocclusion very similar to ours. The influence of socio-economic factors on the children's health was reported for caries, nutrition and mental development (5).

VII CONCLUSIONS AND IMPLICATIONS

The recording of prevalence nature background, and associations of physical health problems in a preschool child population is of real interest only when the experiences and results can be applied in practical routine work to improve Child Health Services. It is necessary that research is built in to the planning of health services. Research and planning are both indispensible elements in the creation and maintenance of an effective service In the report from the extensive study of children on the Isle of Wight (59) this view is expressed in the following way "In the absence of research we can only move forward blindly able to profit neither from our mistakes nor from our successes Research and planning need to go forward hand in hand so that the questions for research can arise from problems in service provision and the findings from research can be taken into account when planning further services." This outlook may also be twisted into "All action that is unevaluated is an experiment but carried out in such a way that we cannot learn from the experiment" (30).

The necessity of a "production control" has largely been overlooked in Child Health Services, and very few efforts have been made to evaluate what is really done and accomplished in the daily routine work at the Child Health Centres.

In certain respects the present study provides such an evaluation By a thorough and comprehensive point examination of the total preschool population at the age of 4 years the ability of the existing services to detect and provide care for important health problems could be assessed At once it could be concluded that these services function very well in selected fields of child health but that other fields of physical health are not covered, mainly dental disorders, vision and hearing defects and bacteruria For the time being, however no safe and simple screening methods exist for detecting visual and hearing disturbances or bacteruria until the child is able to cooperate i.e at the age of 3—4 years Dental health has hitherto been badly neglected as is shown by the fact that the vast majority of the children in our study had caries, and that a considerable number were designated as emergency cases.

The dental study (Paper IV) also shows that the introduction of rather simple preventive measures at an early age can produce a significant reduction in caries at the age of 4 years. Therefore another conclusion is that a program for caries prevention must be included early in the general health services for children where an extensive proportion of the population is reached. The design and content of such a program is outlined in Paper IV and it is now being introduced all over the county

For vision hearing and urine testing, methods and procedures have been evaluated From this evaluation and from the findings in the study it may be concluded that screening of vision, hearing and, for the girls, bacteriuria are important items to include in the routine health services and that 4 years is a suitable age to perform this screening, which however should be repeated when the children begin school

It does not seem motivated to perform screening for proteinuria or hyperglucosuria at the age of 4 years.

The results of the paediatric examination were rather sparse Only 2.7 % of the children had newly detected important health problems at this examination (left part of Fig 2, Table 13) and although they are considered important, they are not handicapping to the same extent as the disorders already detected (Paper I Tables 1 3–4 9–11). Under these circumstances the question may be raised as to whether a thorough clinical examination by a paediatrician is a necessary or worthwhile procedure in a health control of this kind. Much time money and effort could be saved if some form of screening could be applied between the child and the physician also regarding these types of physical disabilities.

This type of screening could be made by delegating the initial health appraisal to nurses or other health workers. Several studies on adults (31) and children (9 51 64 65) have demonstrated that such physical appraisals can be as effective or even more effective than those made by physicians. Also questions posed to parents teachers or to patients themselves on printed questionnaires or by non-professional interviewers have been able to identify subjects at high risk of having health problems (17 75) The questionnaire used in the present study (see section V 1

pages 14–15) undoubtedly gave much valuable information about the children and their back ground and also identified some children "at risk" However it was found that the questionnaire in the present form was not selective enough to be suitable as a screening instrument.

There are other aspects of the medical examination than the mere case-finding to be considered, aspects that are not easily measured or evaluated A personal contact was established with the children and with the parents, many of whom had not visited a Child Health Centre for a long time Advice support and treatment were offered for minor health problems and since problems perceived as relevant by the parents, whether they are or they are not in objective medical terms appears to be important to the child (?4) it could well be that patient satisfaction and relief of discomfort were valuable outcomes of this medical examination.

These more subtle aspects of health care are not necessarily neglected, if some of the work the paediatrician is now doing is done instead by specially trained nurses, using structured forms and manuals for interviews and for physical examinations

A study of the efficiency and acceptability of such a program is now being performed in Lund and Dalby

This kind of health appraisal could probably be used for other ages also and the paediatric resources could be saved for more urgent tasks, e.g. examining newborns and infants.

The few cases of mild anaemia (0 9%) do not motivate that hæmoglobin measurements are performed as a routine at this age This investigation should instead be saved for children with anamnestic or clinical suspicions of anaemia.

The behavioural aspects of child health and its relation to physical deviations are not mentioned here since they will be the subject of separate reports to be published shortly (35 36). However the need for advice guidance and assistance in matters of up-bringing is great, and since this is also a neglected area of child health services a reinforcement and enlargement of these activities will be an urgent task for the future services (34 37).

If the health control gave many valuable results from the point of view of the "producers of child health services, it was also highly esteemed by the "consumers" clearly shown by the high rate of participation. The uncooperative families were few some of them moreover having acceptable reasons for not participating.

However since it was found in the examination that children from lower socio-economic groups ran a particular risk of having important health problems and since the non-participating families had a poorer socio-economic background, it is concluded that still more effort must be made to encourage all families to participate in the Child Health Services throughout the children's preschool years.

A study like this will answer some questions about child health and its services, but it will also unevitably give rise to many other questions and be an incitement for further research. Thus, a follow-up of these children when they begin school at 7 years of age will provide us with valuable information and serve as a further evaluation of the health control at 4 years of age A follow-up of children treated for significant eye disorders offers unique possibilities for assessing the value of early treatment and for evaluating the proposed classification of eye disorders. A follow-up of the children with malocclusion e g. at ten years of age could provide valuable information about the persistence of malocclusion and its relation to sucking habits Introduction of health appraisal by nurses as discussed above must be evaluated.

The possibilities of detecting functionally important health problems at an even earlier age could be investigated by reviving the concept of "newborns at risk" using a more structured and standardized classification at birth and then examining the children at 4 years and at 7 years of age

These research projects are now being realised at the Child Health Service in Lund.

The important question as to whether the results and experiences of this local study are applicable to other parts of the country or to the whole country was briefly discussed in section 10 1 It was found that the structure of the society the level of education and the social conditions of Lund and Dalby differed from those found in other parts of the country and therefore that the findings of child health in these areas may not

simply be generalised to other areas. The results from other smaller pilot studies of the health control all performed in cities with good opportunities for specialised medical care (5 74) are largely similar although they may differ in detail. Is is probable that the health of preschool children in more densely populated areas does not diverge too much from the picture given in this study Comparative studies from greater rural areas are still lacking, however The organization of this study with its centralized investigations may be suitable in medium-sized communities with good communications. In big cities or in sparsely populated areas, other types of organization may have to be considered.

The most important conclusions and implications from this study may be summarized as follows.

1 In contrast to the ordinary Child Health Services for preschool children this health control succeeded in achieving a very widespread participation presumably by offering an investigation that was recognized by the parents as being important for their children s health.

2. Still greater efforts should be made to attract the interest of the non-attendant small minority of parents.

3 By screening vision, hearing and, for the girls bacteriuria, a reasonable number of important deviations were detected. The age of 4 years is suitable for this screening, but it should be repeated at school.

4 A program for the prevention of caries should be introduced at the Child Health Services at a very early age The age of 4 years is far too late

5 The thorough paediatric examination revealed rather few children with unknown functionally important health problems especially when compared with the time-consuming and expensive method of examination. Most severely handicapping disorders were already detected and cared for Other methods should be tried to detect children with physical health problems.

6 The questionnaire did select some children at risk of having functionally important health problems but was not selective enough to be of value as a screening instrument.

7 Routine haemoglobin measurements are not necessary at this age

8 Screening for hyperglucosuria, proteinuria and in boys, bacteriuria is not motivated at this age

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Dept f Paediatrics
University Hospital
S-221 85 Lund
Sweden

Key words: Health control, preschool children, non-attendance screening, physical health, vision, hearing, caries, bacteriuria, questionnaire.

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CONTENTS

PREFACE

Unfortunately several of the abstracts came in so late that it was impossible to have them read through for language correction. In others, desirable corrections could not be made as there was not time to consult the author

PRESIDENTIAL ADDRESS

K. TRYGGVASON

From the Department of Paediatrics University of Reykjavik Iceland

Paediatricians from the Nordic countries have convened at three year intervals for more than half a century The purpose of such conventions has been manifold, the presentation of scientific work, comparison of notes and discussion of clinical experiences. Last but not least these meetings have endeavoured to strengthen the feeling of fellowship and the ties of personal friendship

This time the Nordic Paediatric Congress is held for the first time in Iceland, the home of the smallest and the most outlying population in the Nordic community The distance has not discouraged our colleagues from attending this meeting as it may prove to be one of the more populous held so far

Proceedings from former Nordic Paediatric Congresses have been published as a supplement to Acta Paediatrica Scandinavica and this tradition will be respected now The abstracts from scientific papers published represent the standard of the work produced by Nordic paediatricians as well as its variety Nordic paediatrics rests on the foundation of old traditions. Many pioneers in the field of Paediatrics have come from the ranks of Nordic paediatricians during the 120 years since the first paediatric hospital was built in Scandinavia. We shall endeavour to maintain and raise the standard of our profession and the quality of the work produced thereby

The high standard of education and national culture has made the acceptance of medical knowledge by the Nordic public an accomplished fact. Even in Iceland a book on paediatrics for the general public was published in 1856 at which time the total population numbered only 70 000

Today preventive medicine is gaining in importance. The Nordic countries, with their low infant mortality rate, have already realized its significance a long time ago. But all progress in this area as well as others rests primarily on sound scientific development and consequently I want to extend my gratitude to all the many contributors whose sincere and serious efforts have made this publication possible.

PAPERS

PLENARY SESSION I

THE PROBLEMS OF ADOLESCENCE

CHAIRMAN HENNING ANDERSEN

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1 THE HORMONAL BACKGROUND FOR ADOLESCENCE

H. ANDERSEN

From the Children' Hospital, Fuglebakken, C penhagen Denmark

Pubertal maturation takes place under hormonal control. Most endocrine organs show an adolescent growth spurt e. g the thyroid, the adrenal gland, the gonads and — especially in girls — the anterior pituitary indicating changes in their function The primary change in sexual maturation occurs along the hypothalamic pituitary-gonadal axis in a way which is not too well understood. Apparently many of the same activities along this axis take place, but in a much smaller scale, in prepuberty and even in fetal life. However other functions, for example, the increase in luteniz ing hormone secretion associated with sleep seems to be specific for the adolescent period. Precisely why and how the different changes in endocrine functions during adolescence take place is not known, but progress has been made during recent years Time of matura tion, sex and perhaps some sexual behaviour may be imprinted on the fetal brain. At least this holds true in some experimental animals. Improved methods for hormone analyses have shed more light on the sequences of hormonal secretion, interactions and relationship to some of the morphological changes observed during adolescence. The first part of this paper will deal with some of these more recent discoveries, especially in boys, since the following paper by Kantero and Widholm will be about pubertal girls.

The second part of the paper comprises some practical approaches to the diagnoses and treatment of retarded and precocious pubertal development and too small or ex cessively tall adolescents.

2. ENDOCRINE MATURATION OF ADOLESCENT GIRLS

R. L. KANTERO and O WIDHOLM

From the Children Hospital and the II Department f Obstetrics and Gynaecolgy of University Central Hospital Helsinki, Finland

This paper is concerned with, and draws con clusions from, the following phenomena connected with puberty in girls

a. Growth, by weight, of several endocrine organs continues according to earlier studies rather far into late puberty i.e. up to the 20th year of life.

b The order and time of appearance of physical signs of secondary sexual development conform to a known pattern. Development of girls is described on the basis of a study of 8000 Finnish girls made in 1969 The mean age of menarche is 13.2 years.

c. Menstrual pattern according to post menarcheal age is described. In the great majority of girls menstruation becomes regular only 2—3 years after menarche. Even in girls who have menstruated for over five years the cycle is more irregular than in adult, parous women Dysmenorrhoe and premenstrual tension increase with postmenarcheal age and their frequency is high five years after menarche. These facts are regarded as indicating that endocrine maturation extends over a fairly long time after menarche.

d. Knowledge about the excretion of various hormones during puberty is still partly obscure. One of the most important reasons for this is that longitudinal studies with sensitive enough methods have not yet been made. The study presented here is based on a recently completed cross-sectional study of 146 healthy girls and young women.

Increased excretion of gonadotropins is regarded as the impulse to puberty Both FSH and LH can be demonstrated already in early childhood, but their excretion increases in prepuberty FSH reaches adult follicular phase levels in girls before LH the excretion of which still increases after menarche. The excretion of steroids (oestrogens, 17 ketosteroids) increases from the beginning of puberty to 4—5 fold amounts when girls with a bone age of 8 years are compared with adult women. The excretion of 17 hydoxycorticoids reaches adult levels already in girls with a skeletal age of 13 and is assumed to correlate to the increase in body surface.

In the serum levels of alkaline phosphatase and growth hormone (GH) a rise is observed coinciding with the period of fastest height growth It is possible that GH plays a part in the growth spurt.

The level of progesterone does not generally rise significantly until about two years after menarche

Also the function of the thyroid is involved in puberty An increase in T_4 and free thyroid hormone level which is not dependent on binding proteins and a significant elevation of serum TSH seem to be in some way involved in the maturation process in girls.

When girls are studied in groups with the same level of skeletal maturation it is found that menarche is not associated with a sudden rise in the excretion of any hormone. Endocrine maturation is a slow almost linear process and final maturity is not reached before about the 20th year of age.

3 THE AGE AT MENARCHE — IS IT STILL FALLING?

G HARLEM BRUNDTLAND and L. WALLØE

From Oslo City Health Department Section fo School H alth and the Departments f Physics and Physiology University f Oslo, Norway

The menarchal age has been progressively falling in all parts of Europe, North America and Japan during this century (1)

From Norway Sweden, Denmark and Finland data are available that suggest this trend can be traced back to the middle of the last century (1)

In Norway three large studies have been

conducted, all in same geographical area, the city of Oslo, data having been collected from all schools through the School Health Services.

In each study the girls were asked whether or not they had experienced their first menstrual period — the *status quo* method. The same is true of a smaller study from 1919 also included in table 1

In Oslo in the period from 1918 to 1952 the average decline in the menarchal age was 4.5 months per decade, an observation that agrees well with results also from countries outside Scandinavia (2) Extrapolation of this trend to 1970 would predict a menarchal age of 12.6 years

The Oslo investigation in 1970 showed, however no change at all during the preceding eighteen years, i.e a complete halt in the trend towards earlier physical maturation (2)

From the two neighbour countries Denmark (3 4) and Finland (5,6) comparable data are available, as shown in table 2. The data from the urban districts of Finland in the first study and those from Helsinki in the latest, have been chosen for better comparison with the Oslo and Copenhagen samples.

The halt of the trend towards earlier maturation, found in Oslo during the period 1950 to 1970 has not been observed in the other two nordic capitals.

When comparing the mean menarchal ages around 1950, Oslo girls were clearly ahead, by 4—5 months, a distance which now has been eliminated.

It remains to be seen whether the same levelling off of the trend towards earlier maturation will be demonstrated in our neighbour countries, with a twenty year lag, which seems to be a reasonable guess.

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Table 1 *Menarchal age in Oslo*

Authors	Year of study	Number of girls	Age at menarche
Schiøtz, 1919	1918	177	14.57*
Schiøtz, 1930	1928	9169	14.18*
Letting, 1956	1952	11618	13.27*
Brundtland & Walløe, 1973	1970	7155	13.24

Recalculated from original tables, using same numerical method as in 1970

Table 2. *Menarchal age in Denmark and Finland*

Authors	Year of study	Denmark		Finland		Norway	
		No of girls	Age at menarche	No of girls	Age menarche	N of girls	Age at menarche
Bojlén et al, 1954	1948—50	17985	13.8				
Simell, 1952	1950			1713	14.08		
Letting, 1956	1952					11618	13.27
Andersen, 1968	1963	532	13.1/4				
Kantero & Widholm, 1971	1969			4104	13 10		
Brundtland & Walløe, 1973	1970					7155	13.24

4 UNDESCENDED TESTIS (CRYPTORCHIDISM)

P E. WAALER

Department f Paediatrics, University f Bergen, Bergen Norway

In the present paper the designation *undescended testis* is preferred as the most adequate term to cover all types of testicular maldescent. Special attention will be paid to problems of practical interest, mainly diagnosis and treatment, which are still matters of considerable controversy

The location of the undescended testis is said to be the point nearest the scrotum to which the testis can be manipulated by clinical examination In clinical work the locations define the different subgroups of undescended testis. The patients with anorchia may also be included as a special subgroup because the presenting problem in prepubertal cases is that of undescended testis.

A thorough clinical examination is of major importance. Retractile testes should be excluded. The clinician should also be aware of the frequent combination of testicular maldescent with inguinal hernia. Persistent processus vaginalis should be suspected when an inguinal testis can be manipulated to disappear into the inguinal channel. In some cases it is difficult or impossible to find both testes by clinical examination. A gonadotrophin stimulation test (4) may then be helpful The Leydig cells of prepubertal boys are relatively dormant and in our experience 3 weeks stimulation with human chorionic gonadotrophin (HCG Total dose 9000 IU) yields adequate testosterone response.

The diagnostic value of testicular biopsy material is highly appreciated by several investigators. Bouin s or Stieve s fluids should be used for fixation of the biopsy Histologic examination forms the basis of a correct diagnosis and gives an impression of the prognosis. Moreover in some bilateral cases from our own series biopsy examination of the testis first operated was of great help in deciding whether or not orchiopexy should be performed on the contralateral side.

It is generally accepted that the undescended testis should be brought to a permanent scrotal position before puberty but the optimal age and the methods of treatment are still matters of considerable disagreement. The aim of treatment is to secure normal spermatogenesis and fertility The evaluation of different systems of treatment in this respect is difficult but considerable evidence has been collected in recent years indicating that early treatment (*i e* before 5—6 years age) yields the best results This view is supported by several histological experimental and follow up studies (1 3 5)

In our own series 12 unselected patients were operated in midpuberty or late puberty Three of the cases were bilateral. In 10 of the testes from this series histological examination showed complete absence of germinal elements (germinal aplasia) The other 5 showed severe impairment of spermatogenesis. In contrast to this uniform picture numerous biopsies from our prepubertal patients showed great variations from an apparantly normal picture through varying degrees of impairment to germinal aplasia. Our results strongly indicate that untreated testicular maldescent results in a gradual impairment of the germinal elements during prepubertal years.

The value of hormonal treatment is a matter of debate. Several authors prefer HCG as the first treatment of choice. In the present work such treatment was successful only in a few cases. In our opinion the following guideline should be followed

Treatment should be finished at about 6 years of age or as soon as possible after this time Primary orchiopexia should be performed in cases with accompanying hernia

when the diagnosis is settled, in cases with a high position of the testis and usually when an open processus vaginalis is suspected. Hormonal treatment may be tried in moderate prepubertal cases. If maldescent is still present 2—3 months after hormonal treatment the patient should be operated on.

In the present series numerous patients were referred for the first time in late childhood or in pubertal years. In our opinion treatment of this age group is of limited value. On the other hand selection of some of these patients for treatment is very difficult and we therefore routinely use operative or hormonal treatment in all cases.

In our experience the combination of testicular retention and hernia is frequently accompanied by a short spermatic funicle. In these cases the usual operative method may result in a too high position of the testis postoperatively. In some of our cases a second operation was necessary and in a few patients a special long loop technique (2) was tried with a good primary result. It is to be hoped that further improvements of the operative technique will lead to better primary and long term results.

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5 PSYCHIATRIC ASPECTS IN TEENAGE MEDICINE

M. FRISK

From the Department of Child and Youth Psychiatry University Hospital Uppsala Sweden

6 PROPHYLACTIC ASPECTS OF NARCOTIC MISUSE AMONG TEENAGERS

M. KIHLBOM

Psychiatric Clinic for Children and Adolescents St Görans Hospital Stockholm

The misuse of narcotics by an individual is a late stage in a long process of psychological development, both individual and social. In

of the young individual's self-evaluation and identity becoming more and more unfavourable for constructive solutions of various pro-

and for the constructive satisfaction of emotional needs (such as a sense of belonging, of being appreciated) Secondly the environment not only creates conditions which place obstacles (such as anonymity in large groups, the generation gap extensive use of alcohol and psychopharmacopoeia) in the way of such constructive solutions, but also takes measures which confirm and reinforce the drug abuser's negative opinion of himself (such as various types of rejection from family or peer groups)

We know from a number of studies that whereas many young people experiment with drugs only a few continue using them, and many of these give them up spontaneously In the drug abuser's development we regularly observe a spiralling process from emotional difficulties via behaviour problems to rejection new emotional difficulties, new behaviour problems, new rejections, and so on.

Preventive measures will thus to a great degree coincide with mental health work in its broadest aspect, and thus with socio-political, family welfare and psychological measures.

7 THE ADOLESCENT UNIT A NEW AND NECESSARY PART OF THE PUBLIC HEALTH SERVICE

O WASZ-HÖCKERT

Department of Paediatrics, University of Helsinki, Finland

In order to fill the needs for special health services in adolescence, not properly given by either pediatricians or internists, an initiative was taken by Roswell Gallagher and the Adolescent Unit was initiated in Boston 1951 These services exist today at most universities and larger medical centers in USA on an outpatient basis and in addition to that an increasing number of centers concentrate hospitalized patients from this age group in special adolescent departments.

In Helsinki an Adolescent Unit was founded 1962 by Folkhälsan, working on a rather scientific basis, as publications by Frisk, Widholm and Hortling indicate. Shortly after that the Mannerheim League founded similar units in other cities, too, supported by private funds. Now this kind of outpatient station for adolescents exists in some major cities as a part of the Finnish public health service

In order to make services easily available for adolescents, these units are outside hospitals in the main city area, they are free of charge and open in the afternoons and evenings.

The team consists of physicians, — specialized in this age group — social workers, psychologists, youth-psychiatrists and consultants (gynaecologist, dermatologist, endocrinologist etc.)

Most of the adolescents come on the recommendation of friends or on the initiative of school health authorities, parents or teachers.

The team has to be especially familiar with all the problems there are in this age group The work must be based on a good physical check up, although the majority have psychological or minor psychiatric problems. Severe narcotic problems e.g must be sent to psychiatric or special narcotic clinics.

Experience from Finland shows that this age group really needs special service from public health authorities and we do recommend it also for other Scandinavian countries

THE INFLUENCE OF PSYCHOLOGICAL FACTORS ON PRESCHOOL CHILDREN

CHAIRMAN PETTER KARLBERG

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8 MOTHERS AND THEIR FIRST BORNS

E. LAGERCRANTZ and R. LAGERCRANTZ

From the Departments of Obstetrics and Pediatrics, Karolinsk Sjukhuset Stockholm Sweden

This study was undertaken in order to try to diagnose mothers in the maternity unit in need of help in their adaptation to mother hood and nursing A random sample of 33 healthy primiparae who had had normal pre gnancies and deliveries and had given birth to full term, healthy babies has been studied by a child psychologist and a pediatrician Mothers were interviewed with a tape recor der and a semistructured questionnaire three days after delivery In a pilot-study it had become obvious that mothers eagerly wanted to discuss their experiences during labour Given this opportun ty they gave detailed and open reports on thei situation and earlier history All mothers and their babies were observed during several hours (esp during feeding and nursing) by other psychologists. Their behaviour and interaction was regi stered and graded according to «quality (tenderness, warmth etc) Mothers were tested w th Rorschach and all babies were repeatedly examined by the pediatrician. In the follow-up all mothers were home visited, again nterv ewed and observed in their inter act on with the babies when the children were 1½, 4 6 and 18 months old. The children were examined and tested with Griffith devel opmental scale Social backgrounds, condition and changes were noted. Fathers were inter viewed by a child psychiatrist.

Some of the results will be reported and discussed A great span of different experi-ences, attitudes, behaviour and developmental patterns was observed. According to mothers adaptation to motherhood and childrens development three or five groups could be formed. A group with good adjustment was characterized by good family background with good relationship between mother and her own mother (child s grandmother) good relationship to father planned or well ac cepted pregnancy good psychic health during pregnancy and positive experience of labou and relatively quick adaptation to infant's needs already in the maternity unit. At the other end of the spectrum women were ob-served with great difficulty in adaptation to motherhood and with children with unsatis-factory or poor development.

These women most often had an unfavour able family background poor or hostile re-

lationship with their own mothers, had not planned and not accepted pregnancy had had many disturbing psychic symptoms during this period and had experienced labour as a shock with high anxiety and tension. In the maternity unit they had great difficulty in accepting or enjoying their motherhood and responding to the basic needs of their newborn babies.

The results seem to indicate that it is possible to diagnose in the maternity unit a group at risk for child abuse and in great need of help, support and training.

9 THE SECOND DEFENCE LINE

A. GRUDA SKARD

Instit of Psychol gy University of Osl Norw y

Right after birth the baby is dependent on its mother for its food and in our culture mostly for care, and human contact. However the development of independence, distance and wider sozialization goes on gradually and at varying speed all the time. Mother and child do not live in a vacuum they are surrounded by a physical and human world. The child is influenced directly and indirectly by not least other human beings, — the father grand parents, older siblings, neighbours. These per sons will be a) meaningful for the mother child relationship b) meaningful for the child by their direct interplay with it.

The father offers the mother security (or not) emotional stability (or not), periods of relaxation, rest and opportunity for contacts outside the home — all of which will be of importance to the mother s attitude to the child. Directly he gives to the baby a different set of stimulations by his handling the child, speaking with a masculine voice, lau ghing touching and carrying the baby in his own way

The grandparents, as well as uncles and aunts and close friends of the family surround the nuclear family with additional security presenting possibilities for the child as well as for its parents to serve as a second defence line» to which one may resort in various kinds of crises. The role of e.g grandparents should be taken into account to a higher degree than our psychological literature has so far allowed us to do The role of older siblings has been discussed mainly in terms of jealousy rivalry and negative experiences. However,. the components of protection open emotionality in child-child relationship, confidence, interplay even mutual support in the reactions towards adults might be discussed.

Even in the child s first year of life its relationship is not limited to the mother nor even to the parents. The formation of a grow ing personality is influenced by the total group of persons surrounding the baby at close quarters (parents, siblings) and at somewhat greater distance (grandparents, aunts, uncles etc.) all of them contributing to the baby s feeling of security its experience of early stimulation, its perception of human relations and its awareness of expectancy reward, and disapproval of his own reactions.

10. DISCIPLINARY METHODS IN PRESCHOOL CHILDREN

I. KLACKENBERG-LARSSON

11. EDUCATION OF PRESCHOOL CHILDREN — A PEDAGOGIC ANALYSIS WITH PAEDIATRIC ASPECTS

E. M. KØHLER & L. KØHLER

12. CHILD UPBRINGING IN THE NORTHERN REGIONS

H. FORSIUS

13. LONGITUDINAL ASPECTS OF BEHAVIORAL SYMPTOMS IN RELATION TO SOCIAL FACTORS

G. KLACKENBERG

14. PSYCHOSOCIAL FACTORS IN CHILD MORTALITY IN A WELFARE SOCIETY

G. VON SYDOW

15. FOUR YEAR-OLDS IN A NEW SUBURB. THE NEED OF MEDICAL AND SOCIAL CARE

B. LAGERKVIST, S. LAURITZEN, P. OLIN and K. TENGVALD

From the Dept. of Paediatrics, S:t Göran's Children's Hospital, Child Guidance Clinic and Socialhögskolan, Stockholm, Sweden

Standardized health examinations for four year-olds have been used in Sweden since 1968 to trace children with physical, mental or social problems. Previous studies in Dalby (1), Uppsala (3) and Gothenburg (2) showed that in general the four year-olds received adequate

medical care. Their mental and social circumstances, however were insufficiently known. Therefore a study of the four year-olds in a Stockholm suburb was performed in 1972 This newly erected residential area comprised 15 000 inhabitants in 1972 and is made up of apartment houses compactly grouped around mainly hard-surfaced play areas, well separated from the vehicle traffic. Here live mainly young families with children predominantly of pre-school age and the per centage of immigrants is above 25

The investigation was performed mainly according to the recommendation of Social styrelsen (4) The total population of residing four year-olds as located by manual search of well-baby-clinic-charts and the local church register as well as by check lists from the county register was 293 of which 255 or 87.2 % underwent a complete examination Thirteen children, 4 %, refused to partici pate, and five, 1.7 %, were not known to the well-baby-clinic. The refusers» belonged mostly to families with social or medical problems and should be considered as a risk group

The results showed that 23 % of the chil dren had caries. Medical problems led to 64 referrals, thus 20 children were referred to ophthalmologists (7 8 % of the children) and 18 to pediatricians (7 1 %) The remaining 26 referrals involved pediatric surgical, otolaryngological orthopedic, and phoniatric problems.

Of the 255 examined children 176 (69 %) were staying at their home during the day 34 (13 %) were four to eleven hours in a family day-care home, and 45 (18 %) were in day nurseries. The parents of 176 (69 %) were both Swedish, whereas one or both pa rents of the remaining 79 (31 %) were immi grants. The 44 (17 %) Finnish children con stituted the largest foreign group Twenty nine children of immigrants did not speak Swedish. Two of them had one Swedish pa rent. Only four of the children that did not speak Swedish were cared for in day nurseries.

Mental problems led to closer follow-up at the well-baby-clinic for 58 (22.5 %) children and referrals for further psychological work up for 29 children (11.5 %) Among the latter only two concerned day nursery children (total 45) the remaining 27 concerned children who stayed at home or in family day care (total 210) The child psychologist recommended early admittance to organised group activities with other children for 21 out of the 27 children. Among those who were recommended follow up at the well-baby-clinic an additional 27 home- and family-day-care children were recommended early pre-school admittance at the examination predominantly because of signs of withdrawal or understimulation The total number requiring early preschool or nursery activities amounted to 72 children, or 35 % of the home- and family day-care children, including the 25 immigrant children that did not speak Swedish.

In summary the day nursery children appeared to have less mental and language problems than the home- and family-day-care children. Among the latter a pressing claim for increased stimulation earlier than the general pre-school for the six year-old is demonstrated. An inexpensive daily group ac tivity for three to five-year-olds, involving the parents as co-leaders, is tried as one of several means to meet this demand

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16 THE GOODENOUGH DRAW A MAN TEST IN 358 FOUR YEAR-OLD SWEDISH CHILDREN

F GYULAI

From the Central Hospital, Gävle, Sweden

This test is a part of a detailed physical and developmental check-up of all four year-old children in Sweden — The results from 358 children, aged 4—4¹/₄ and living in Söderhamn, a town with a population of 13,000, from the period April 1970—May 1972, representing 96 % of all children in the resp age groups, are described.

All tests were administered and evaluated by the author For each drawing, the »raw score» i.e., the number of items, was determined according to Harris, 1963 — As regards social data, about half of the parents were manual workers, ¹/₄ salaried employees, 5 % professionals and about as many had enterprises of their own. About half of the mothers were housewives, 20 % had a part time job outside home and somewhat fewer a full-time one. No significant differences in these respects were found between the parents of the boys and those of the girls.

RESULTS

Of all children 79 % were able to draw a human figure, 10.6 % were not and 10.3 % did not cooperate. However the performance of the girls was much better than that of the boys: 87 4 % of the girls were able to draw a man as against 70.3 % of the boys (Fig. 1) Moreover of those children who could draw girls reached a higher mean score (7.8/SD:1.3) as against 6.3 (SD 1.5/for boys) (Fig 2)

Further sex differences a) All items except legs were drawn more often by girls than by boys, b) especially large differences (girls boys = 2 1) were found with regard to the feminine items» described among others by Harris for somewhat older children than ours (hair details of the eyes and clothing) but also with regard to ears (girls 13.7 %, boys 7.3 %) c) of the qualitative items (Harris, 1963), only seven are found in these drawings — there was 0.5 such item/boy and 0 9/girl.

Expected items (= present on 86—100 % of the drawings, E. Munsterberg Koppitz, 1968) are head and eyes, common items» (51—85 %) include legs, mouth, nose and body for girls and legs, month and body for boys.

On the basis of a detailed anamnesis and of observation during a check-up of sight and of motor function, 12 boys and 4 girls were classified as showing some lag of psychomotor — mental development. (Out of these, 2 boys and one girl showed signs of moderate mental retardation.) Of those who were able to draw a human figure, only 2 boys (1.6 %) and one girl (0 6 %) belonged to this group of the 29 boys and 10 girls who were unable to draw eight (27.6 %) and three (30 %) respectively

The ability to recognize quantities up to three was tested by asking the children to

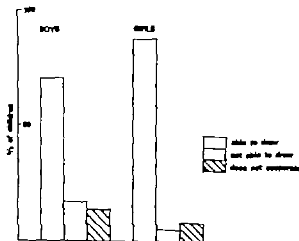


Fig 1 The ability to draw a human figure (at least 3 items) in 175 boys and 183 girls of age 4—4¹/ years.

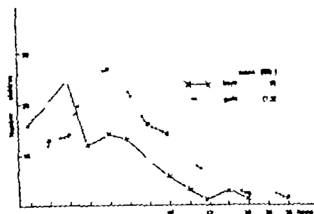


Fig 2. Distribution of number of items on the drawings of 123 boys and 160 girls. / of children

give the correct number of three pencils and three coins. Although the material is too small for statistical analysis, the results show some positive correlation between this test and the draw a man test of 123 boys who could draw 51.2 % could count, of those 29 who were unable to draw only 31 %. Of 160 girls who could draw 59.3 % could count, of those 9 who could not draw only 22 %.

No significant correlation was found between the occupation of the father and the result of the test. However the reason for this might be the low number of some occupational groups — The home situation of the mother (working or not working outside home) did not influence the results.

The observed differences in performance at the draw a-man test between boys and girls at the age of 4 are in agreement with the results of others (Harris, 1963 Munsterberg Koppitz, 1968) as well as with results of other tests of psychomotor development (Karin Stensland Junker 1972) They show that significantly less achievement in this test is to be expected of boys than of girls in this age group

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17 SECULAR TREND IN THE GROWTH PATTERN OF NORTHERN CHILDREN WITH SPECIAL REFERFNCE TO PRESCHOOL AGE

J TARANGEP

18 HEIGHT WEIGHT AND HEAD-CIRCUMFERENCE IN WEST-GREENLANDIC CHILDREN

B. ZACHAU-CHRISTIANSEN

Child H alth Clinic University Hospital (Rigshospitalet), C penhagen, Denmark

During a course in 1970 for the Greenlandic public health nurses instruction in height and weight-measurement together with measurement of head-circumference was given

In the following two years heights and weights for 945 infants and children from the neonatal period until age 16 were recorded the head-circumferences only in 248 cases.

These measurements were obtained from Umanaq Christianshåb, Godthåb, Narssaq Julianehåb and Nanortalik. In accordance with the instructions only children of Greenlandic parents were investigated

Until the age of 2 years the heights were found to be within Scandinavian norms as used in the University Hospital, *Karlberg & Perman* (1959) After age 2 nearly all values are placed between m and m 2s, the height means in different ages being approx. 5 cm lower than the used norm.

A diagram of height to weight shows that from 90 to 140 cm the weights are distributed between m and m+2s, over 140 cm the weights are placed near to the m-curve with a very short range, under 90 cm the range corresponds to ± 2s.

The head-circumferences until 2 years of age are distributed within the 10- and 90-percentiles in the norm ordinarily used.

19 HEIGHTS AND WEIGHTS IN DANISH SCHOOL CHILDREN AT THE PRESENT TIME

E. ANDERSEN H. ANDERSEN B. PEITERSEN J ROSEN
L. THAMDRUP and R WICHMANN

Children Hospital F glebakken Copenhagen Denmark

No large scale examination of height and weight has been made in Denmark since Dossing s measurements of children (1932—1942) It is therefore desirable to obtain current figures of height and weight in Danish children

Data is presented giving both heights and weights and increments in heights and weights for a normal material of Danish school children aged 7—18

The material consists of 5,500 boys and 5,500 girls chosen from the Danish school population in such a way that each child within a given age group has an equal chance of being selected. For each child the measurements are taken from that child s school health record for 1971 and 1972.

The material is geographically representative of the whole country enabling urban rural comparisons to be made.

SESSION I

NEONATOLOGY

CHAIRMAN BENT FRIIS-HANSEN

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20 NEONATAL HYPOCALCEMIA (NHC) IN INFANTS OF DIABETIC MOTHERS (IDM)

L. BERGMAN, I KJELLMER and U SELSTAM

Department of Paediatrics Children' Hospital University / G theaborg Gothenburg, Sweden.

Infants of diabetic mothers (IDM) have a greater risk to developing NHC than normal babies. To test whether this hypocalcemia is related to a release of calcitonin (CT) triggered by a primary increase of glucagon because of the hypoglycemia, the concentration of CT in blood was determined in a group of normal infants.

From May 1 to December 31 1972 total calcium (Ca tot) ultrafiltrable calcium (Ca-uf) phosphorus, total protein blood sugar and calcitonin in plasma have been determined at different time intervals from birth up to 48 hours of life in 6 unselected IDM and 6 normal infants Calcium and phosphorus excretion in the urine were measured in the IDM. Ca uf was determined by the method of Bergman Isaksson (1) and each value was corrected to the actual pH of the infant.

At birth no significant difference in either Ca tot or Ca-uf between the two groups was observed. After birth a decrease was seen in Ca tot and Ca-uf in both groups, being more marked in IDM.

The differences between the two groups in both Ca tot and Ca-uf at 24 hours of life were highly significant From 24 hours an increase of Ca-tot and Ca-uf occurred in both groups and at 48 hours of life there was no significant difference between the two groups.

Two of the IDM developed clinical symptoms of NHC when Ca-uf decreased below 5.0 mg per 100 ml plasma. When Ca-uf increased above 5.0 mg per 100 ml plasma the symptoms subsided. The presence of hypoglycemia was excluded. Phosphorus showed a tendency to increase after 12 hours of life. No significant differences in the phosphorus concentrations were found between the two groups at birth, at 24 hours or at 48 hours of life. Blood sugar decreased in both groups but more markedly in IDM

The concentration of CT increased markedly after birth. The maximum values were 2—8 times the umbilical vein concentration in IDM and 6—10 times in the normals Two exceptions were seen One IDM and one normal infant had only a slight increase of CT concentration. The increase in CT started already at 5—6 hours of life and maximum was reached at 24 hours of life, after that the concentration decreased. No significant difference in the CT concentration was seen between IDM and normals.

The concentrations of calcium and phosphorus in the urine were negligible up to 24 hours of life After that an increase was seen in the phosphorus concentration in 4 of the IDM up to 48 hours of life while the concentration of calcium remained negligible. This is in agreement with the findings of Tsang et al. (3)

A positive correlation was seen between the weight of placenta and both Ca tot and Ca-uf in umbilical vein and between the weight of placenta and the decrease in Ca tot and Ca-uf from birth to 24 hours of life. This might indicate that the initial decrease of calcium concentration after delivery is caused by the loss of the active transport of calcium through placenta, a theory which has been suggested in the liturature

The value of Ca-uf of 5 0 mg per 100 ml plasma has in previous studies (2) been shown to be a critical level at or below which clinical signs of NHC appeared This value also seemed to be the same critical limit for IDM.

The study does not support the hypothesis that the NHC of IDM is related to an increased release of calcitonin.

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21 CRY ANALYSIS IN CONGENITAL HYPOTHYROIDISM AN AID TO DIAGNOSIS AND CLINICAL EVALUATION

L. VUORENKOSKI V VUORENKOSKI and I ANTTOLAINEN

Department of Paediatrics Keski-Pohjanmaa Central Hospital, Kokkola Finland and Dept of Speech Communication, Royal Institute of Technology (KTH) Stockholm, Sweden

A harsh, low pitched voice has been mentioned as a symptom in congenital hypothyroidism (1) This voice quality is similar to that occurring in Down's syndrome (5) The aim of this paper is to describe the significance of a specific cry analysis in a case of congenital hypothyroidism.

The patient (a girl) was born at term after an uneventful pregnancy nothing abnormal could be observed after the delivery At the age of 5 weeks the baby was still somewhat icteric and the parents had observed that the cry of the baby was hoarse and voiceless. The baby had gradually become hypotonic and tired and was re-admitted to the hospital at the age of 9 weeks.

The preliminary investigation in the hospital showed that the cry of the baby was similar to that occurring in hypothyroidism, her face was oedemic, her skin was icteric and dry her respiration was noisy and neurologically she was alternatively hypotonic and hypertonic. The laboratory investigation (2) showed a total absence of serum thyroxine

The pain cry analysis (4) performed at the same time revealed a long extremely tense, almost voiceless cry with a low fundamental frequency The continuous cry analysis with CRY DETECTOR (3) showed an abnormally low number of long cry signals with low pitch (194 cries/24 hrs, mean length 1.53 sec) The occurrence of cry periods was not in corre-

lation with the feeding schedule. Already after one week's treatment the clinical picture showed a partial recovery and clear signs of normalization in the cry qualities could be registered by CRY DETECTOR only two weeks after the treatment had been started (3391 cries/24 hrs, mean length 1.26 sec, no cries above 1000 Hz) Since one week from the beginning of the treatment (desiccated thyroid, THYRANON R) the patient's serum thyroxine values have been continuously normal during her first year of life.

A noticeable normalization of the pain cry the spontaneous cry and the respiratory sound could be observed 7 weeks after the treatment had been started the baby was at that time *16 weeks old Her developmental status was* still somewhat retarded and not until the age of 6 months were her neurological development and her bone age within normal limits. Some deviation could still be observed in the cry analysis (hoarseness and long duration of the phonation) the cry and respiratory sound were not normalized until the age of 8 months. The clinical examination at the age of one year did not show any kind of abnormality Her voice was also normal except for the fact that she did not show any tendency to use a pitch above 1000 Hz.

A methodological cry analysis in a patient with congenital hypothyroidism thus showed that the cry analysis may be a valuable device in diagnostics and control of the treatment of this disease.

Acknowledgements

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27 HIGH HEMATOCRIT SYNDROME IN THE NEWBORN INFANT PHYSIOLOGICAL ASPECTS

G. BERGQVIST

Department of Paediatrics St Göran's Hospital Stockholm

Among newborn infants, some groups such as small for gestational age infants, infants of diabetic mothers and the twin transfusion syndrome have very high hematocrits. In connection with this, symptoms of central and peripheral circulatory failure have been described and this has been attributed to the high viscosity of the blood.

A study of blood viscosity in newborn infants reveals an enormous variation, mostly depending on differences in the hematocrit. In infants with increased hematocrit values, the

in vitro viscosity is 3 times that seen in normal adults. Hematocrit values between 55—73 % showed a good linear correlation to viscosity. The effect on peripheral flow of the blood viscosity as measured by muscle flow, lactate and pyruvate production and renal function, however, seems to be complex. Other factors such as blood volume — blood pressure — cardiac output and vasomotor activity have a more pronounced effect on the peripheral blood flow.

23. NEONATAL HYPOGLYCAEMIA

Presentation of 67 patients with follow-up studies

G. FLUGE

From the Department of Paediatrics, University of Bergen, Bergen, Norway

During the three-year period 1967—69 hypoglycaemia was recorded in 67 newborn infants admitted to the Children's Hospital, Bergen. Routine blood sugar determination revealed hypoglycaemia in 50 patients among 323 low birthweight infants (15.4 %) and in seventeen patients with birth weight above 2,500 g. Eighteen patients were small for term, and toxaemia of pregnancy occurred with the same frequency (27 %).

Among 24 infants born to diabetic mothers, seven (29 %) became hypoglycaemic. These patients are not included in the material.

Asymptomatic hypoglycaemia was detected in 13 patients. Only one patient in this group had hypoglycaemia of long duration (7 days). At follow-up he had signs of minor motor defects. Oral glucose tolerance test showed a diabetic pattern.

Patients with *symptomatic hypoglycaemia* were divided into two groups. Eleven patients were classified as idiopathic, transient neonatal hypoglycaemia and these demonstrated favourable response to glucose infusions. In 43 patients hypoglycaemia seemed to be secondary to some other neonatal disorder (asphyxia, brain injury etc.).

In neonates with *idiopathic transient hypoglycaemia* the symptoms usually occurred after the first day and the hypoglycaemia tended to be of long duration. Neonatal convulsions seemed to be an unfavourable prognostic sign. Among 7 patients in this category one died hypoglycaemic, one became severely mentally retarded with spastic triplegia and had infantile spasms at the age of nine months. Another patient developed spastic diplegia, and four had later convulsions. Two of them were hypoglycaemic after the newborn period: one has hyperinsulinism, the other is still under investigation. One patient had optic disc atrophy.

Of 43 newborns with *secondary hypoglycaemia* 17 died during the first four weeks of life. Hypoglycaemia seemed to play only a minor role as a cause of death. At follow-up (21 patients) normal findings were recorded in ten (47 %). No patients in this group were severely mentally retarded, six showed minor motor defects, and one had spastic diplegia. Another patient has a pathological glucose tolerance test with diabetic pattern. Neonatal convulsions do not seem to indicate as poor a prognosis in secondary hypoglycaemia as in idiopathic, transient hypoglycaemia.

24 ASSISTED VENTILATION OF NEWBORN INFANTS

TECHNIQUE AND RESULTS

J Kamper P M Christiansen and B Friis-Hansen.

From the Neonatal Department, University Clinic Rigshospitalet C penhagen Denmark

Since 1953 when Donald & Lord published their first paper on artificial ventilation in neonates with RDS work in this field has spread extensively throughout the world.
From 1966 at Rigshospitalet's Neonatal unit we have made use of the Bird respirator Mark 8 & 10 and more recently (from August 1971) have added CPAP Criteria and indications for assisted ventilation are discussed.

CPAP treatment, in comparison to earlier respirator treatment, has reduced mortality among neonates with RDS and birth weights of at least 1500 g from 51 to 32 ($p < 0\ 05$) This treatment, it must be emphasized, did not make respirator treatment superfluous, as this was necessary in $^{2}/_{3}$ of the primary CPAP treated patients. This relationship will be elaborated.

A combined CPAP respirator system, which allows immediate changes from one ventila tory system to the other is presented, in connection with the department s newest ventilation programme. It is made up of primary CPAP treatment of RDS patients, using the guidelines of arterial O_2 & CO_2 tension, acid base status, as well as esophageal pressure and hemodynamic parameters.

In the case of progressive respiratory insuf ficiency despite CPAP the ventilation treat ment is continued with a respirator delivering a positive end expiratory pressure. This resul tant form can be explained by a combination of SPAP and IPPV (intermittent positive pressure ventilation) The preliminary results of this treatment are presented.

25 STUDIES ON MATURITY IN NEWBORN INFANTS THE VALUE OF FETAL HEMOGLOBIN AND α FETOPROTEIN IN ESTIMATING GESTATIONAL AGE

O FINNSTRÖM, B. ZETTERLUND and B. KARLSSON

Department f Paediatrics University Hospital, Umeå and Inst tute f Zoophysiology University f Lund Sweden

Estimation of maturity and thereby gestational age in newborn infants is of value from several aspects as has been discussed elsewhere (2)

Since birth weight is now known to be an unreliable index of maturity and gestational age there has been increasing interest during recent years in finding and testing new methods for estimating gestational age in newborn infants. Several papers on these estimations have been published. For various reasons it is difficult to evaluate the results of many of these studies (2) At the depart ment of Paediatrics, Umeå, we have therefore

made systematic studies comparing different methods for maturity estimation. The methods earlier studied were anthropometric measurements, external characteristics, neurological tests, examination of epiphyseal centers, motor conduction velocity and sensory conduction velocity (1 2) The best methods were those based on external characteristics and neurological tests, the former being the most suitable for routine work.

We now present results from the work with two additional methods for maturity estimation, fetal hemoglobin and α fetoprotein in cord blood, both of which have been claimed to be of value in this respect (3 4)

60 infants have been examined so far The two methods have been compared with birth weight and external characteristics. Fetal hemoglobin is the best of these two methods, the correlation coefficient being only slightly lower than that for external characteristics. α-fetoprotein correlates less well with gestational age than does birth weight in this study

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26. ATHEROSCLEROTIC CHANGES OF THE ILIAC ARTERIES IN CHILDREN WITH A SINGLE UMBILICAL ARTERY — THE EARLIEST FORM OF ATHEROSCLEROSIS IN HUMANS

W W MEYER and J LIND

Karolinska I st Department f Paediatrics, Stockholm, Sweden, and University f Mainz, West-Germany

The absence of one umbilical artery is associated with an asymmetrical development of the iliac arterial tree At the side of the single umbilical artery the common and the internal iliac arteries — the only connection between the abdominal aorta and the placental circuit — are large and thick walled in comparison with the same arteries of the other side of the body which do not participate in the placental circuit. A striking pathological lesion of the enlarged arteries at the side of the single umbilical artery is the early and regular development of marked intimal lipidosis and atherosclerotic plaques. Since these changes could be found as early as at the age of thirteen months, they represent the earliest atherosclerotic lesions observed in humans so far The evaluation of local structural and hemodynamic factors, which are mainly responsible for the development of these early lesions, may be important for the better understanding of the pathogenesis of human atherosclerosis, especially of its early stages in childhood.

27 ECHO-ENCEPHALOGRAPHY IN THE NEONATAL PERIOD

T VALKEAKARI

Department of Paediatrics University of Oulu Oulu, Finland

Neurological diagnostics in the neonatal period will meet difficulties because of the diffuse symptoms and signs of neurological disorders due to the immaturity of the neonatal brain. As it is considered inadvisable to perform neuroradiological examinations in neonates, there has not been a suitable method of obtaining information about the anatomy of the brain in the first weeks of life.

Echo-encephalography presents a quick and easy method for this purpose. Especially Lithander Sjögren and Dill have investigated newborn babies using the s.c. one-dimensional echo-encephalography or A-scan. Lombrose et al. have published some pictures dealing with the neonatal brain in the two-dimensional method or B-scan which produces a tomogram of the desired plane. The advantages of the B-scan method are a more reliable identification of echoes and an easier exclusion of the artificial ones.

The reactions of the brain immediately after delivery are not known because investigations have not been performed in this field For that reason A-scan and B-scan echo-encephalography examinations were performed on 51 healthy newborns at the ages of 3 6 12 and 24 hours, 2 4 and 6 days. The relationship between the common width of the lateral ventricles and the bitemporal diameter of the head, the s.c lateral ventricle index (LVI) was determined. The mean values of LVI were 0.30—0 32 both in A-scans and in B-scans during the whole first week The values agree with those given by Sjögren and Dill The brain mantle index gave the mean values of 2.25—2.30 in A-scan and 2.36—2 41 in B-scan. The differences are statistically significant and they depend on the difficulties of distinguishing the different components of the end echo in B-scan. The normal range of the midline shift has been considered as 2 mm. It was shown that as many as 10 per cent of the babies had a midline shift over 2 mm, but only one more than 3 mm, during the first week The edema of the scalp which at the test points ranged from 1 to 1.5 mm, was excluded when calculating the midline shift.

The greatest benefit of the echo-encephalography in neonates can be received in distinguishing between a hydrocephalus and a normal condition in a baby with separated sutures. Only a very few of these have hydrocephalus and therefore it would be superfluous and risky to perform PEG in all of them. In cases of meningomyelocele it is possible, by means of ultrasound, to determine the best moment for shunt-operation. Bleeding in cerebral parenchyma may produce midline shift which can be registered On the other hand subdural effusions, especially the double-sided ones, may be difficult to diagnose using ultrasound Lithander has suggested that even effusions of quantity of 20 ml may not be diagnosed Different brain anomalies, e.g. cysts, monoventriculias, hydranencephali etc. can quite easily be diagnosed, especially in B-scan.

Echo-encephalography presents in the neonatal period a quick, safe and comfortable neurological examination method, which can easily be repeated when required without straining the patient.

28 PATTERNS OF COAGULATION IN SICK NEWBORNS. TO BE PUBLISHED ELSEWHERE

P HENRIKSSON & H. EKELUND

Department of Paediatrics Malmö Allmänna Sjukhus Malmö Sweden

29 RELATIONSHIP BETWEEN FEEDING ROUTINE AT THE MATERNITY WARD WEIGHT DEVELOPMENT AND DURATION OF BREASTFEEDING

P DE CHATEAU H. HOLMBERG and J WINBERG

From the Department of Paediatrics and Obstetrics University Hospital Umeå, Sweden

t is quite usual in maternity wards in Sweden o weigh infants before and after a meal and o give additional formula up to a certain quantity

From May 1972 all weighing of infants before and after breastfeeding was omitted, only the morning weight was registered (experimental period)

Supplementary food was given only on medical indications, such as low birth weight, dysmaturity or to infants with evident symptoms of hunger Infants born during a two months period prior to our experimental period were used as a control group

The questions we asked were whether the anxiety brought about by repeated weighing n the maternity ward will influence the onset and duration of breastmilk secretion and whether any appreciable changes of expected weight development would occur

The duration of breastfeeding has been quite the same in experimental and control groups. The lowest weight measured and the weight at the day of departure from the maternity ward (usually day 6) was somewhat lower in the experimental group. At 6 weeks of age the weight was however the same in both groups.

The observations are still going on. It is therefore too early to draw any definite conclusions, but we have observed less anxiety and worry in the maternity ward and the staff has got more time to take care of the mothers. Multiparae have often expressed their satisfaction with the new system.

SESSION II A

NEUROLOGY

The changing panorama f cerebral palsy (symposium)
F ee papers within paediatric neurology

CHAIRMAN: BENGT HAGBERG

30 CEREBRAL PALSY IN EAST DENMARK CHANGING FREQUENCIES DURING THE YEARS 1940—1969 (COMMUNICATIONS FROM THE DANISH CEREBRAL PALSY REGISTRY)

P GLENTING

From the Department f P ediatrics Rigshospitalet Copenhagen, Denmark

31 FIELD STUDY ON THE INCIDENCE AND DISTRIBUTION OF VARIOUS SYNDROMES OF CEREBRAL PALSY AMONG SWEDISH CHILDREN BORN 1959—68

I OLOW B HAGBERG & G. HAGBERG

From the Department f Paediatrics University f Gothenburg, Sweden

Altogether 429 cerebral palsied children born in 1959—68 in the town of Gothenburg the county of Uppsala and four counties belong ing to the Western Region were reevaluated and classified according to the system used in Sweden since 1958 The three materials were considered to be unselected and complete Statistical calculations concerning the diffe- rences between the first and seco d five-year periods were performed on each s drome separately However for the purpo of this particular study spastic diplegia and ataxic diplegia were grouped together The approxi- mate rate of deliveries in obstetric units in Sweden during the years in question was 99 %. During the second five-year period (1964—1968) a significantly decreased total incidence of cerebral palsy was revealed This was found to be due mainly to a likewise significantly lowered number of diplegic babies, and, among them, of those who were prematurely born with a birth weight less than 2 500 g (for further details Ref to Acta Paediat. Scand. 62:xxx 1973)

32 THE SUCCESSIVE CHANGES IN THE SWEDISH PANORAMA OF CEREBRAL PALSY DURING THE LAST 20 YEARS

B. HAGBERG, I OLOW & G HAGBERG

From the Department f Paediatrics University f Gothenburg, Sweden

Recent experience from a field study comprising 4.9 Swedish cerebral palsied children born 1959—68 (Acta Paediat. Scand 62:1973) brought about an expanded investigation for the further analysis of certain trends within the changing panorama of cp-syndromes. In addition to the already demonstrated and significantly decreasing number of prematurely born diplegic babies appearing from the middle of 1960's, the following preliminary conclusions could be drawn.

Spastic hemiplegic syndromes seem to have 'iminished, but it has hitherto not been ossible to demonstrate statistical significance. he small percentage (2—5 %) of severe pastic tetraplegic syndromes has remained naltered, most of these being of prenatal evelopmental origin.

There was a gradual disappearance of pure choreoathetosis due to kernicterus in Swedish babies born between 1950—60, and no single case has been diagnosed in Gothenburg since that time Dyskinetic syndromes due to peri natal asphyxia have remained quantitatively unchanged during the last 15 years in spite of all obstetric and neonatologic efforts. How ever a qualitative improvement might have occurred with a smaller number of very severely damaged children appearing today The incidence of congenital ataxic syndromes has also remained unchanged through the years, while postnatally acquired ataxia and ataxic diplegia due to expanding hydrocepha lus seem to have decreased parallel to the institution of modern active shunt procedures.

33 GENETIC ASPECT OF CEREBRAL PALSY IN ICELAND

R. GUDMUNDSSON

From the Department f Neurology University Hospital, Reykjavik Iceland

\ survey of cerebral palsy in Iceland was erformed and published in 1967 The 10-'ear period 1953—1962 was chosen. The birth ncidence and prevalence rate was on the vhole similar to that of other Scandinavian ind European countries.

In the material of 235 cases, there were six 'amilies with more than one member affected which makes the familial incidence 2.6 cal :ulated by number of families.

Consanguinity of parents was found to be 5 4 per cent n the whole material. In four of the six families, the parents relationship was second cousins or closer

Consanguinity of parents was previously common in Iceland amounting to 3.2 per cent in the whole population and rising to 7 9 in Eastern Iceland during the period 1916—1920 but gradually declining and was found to be 0.3 per cent in the years 1961 1965 which makes the consanguinity in the total material and in the families too, relatively very high In three of the families where the parents were related nothing was found in the

history which was likely to play a role in etiology of the disease except the genetic factor

A unique relationship according to reli able information from family members was found in family no 1 where all four siblings were affected. This family as well as the other families have been explored more thoroughly and will be presented

34 CLINICAL ASPECTS OF CHILDHOOD ATAXIA

Review of a five-year material

O B. SCHJETNE

Central Institute for Cereb al P lsy Oslo Norway

In a retrospective study 59 children are reviewed The patients were examined at the Central Institute for Cerebral Palsy in Oslo during the five-year period 1967—72.

In 42 children (group A) ataxia was the main diagnosis, while the rest (group B) had some other major problem and ataxia as a secondary diagnosis.

The results of this investigation seem to support earlier findings indicating that ataxia is mainly found in children who were born at term birth-weight and length more often above average Inherited disease was supposed to be likely in 25 %, possible intrauterine cerebral damage in 29 %, evenly distributed in the two groups.

In group B, birth traumas were three times more common as cause of the ataxia than in the A group The number of patients born as the first of sibs was also markedly higher in group B, where patients had more serious problems and ataxia only as a secondary diagnosis.

The symptoms first noticed by the parents and leading to the first consultation were most often a remarkable muscular hypotonia (60 %) delayed motor development (50 %) and balance disturbance (30 %)

Varying degrees of mental retardation were diagnosed in 76 % of the cases. 64 % had relatively serious psychiatric problems in need of treatment. A delay in speech/language development in relation to the child s general development state was found in 83 %

The following types of additional handicaps were registered: language/speech disorders, mental retardation, psychiatric problems, impaired vision and hearing additional motor and orthopaedic problems and epileptic fits.

In group A patients were found to have a mean of 3 1 of the above-mentioned serious diagnoses in addition to ataxia, varying from zero — six handicaps per child. In the second group they had from 2—5 additional problems and a mean of 3.5 handicaps per child in addition to ataxia.

The patients seemed fairly well adjusted in their homes. In kindergarten and in school they often had some problems, in relation to friends the adjustment often was regarded as poor

The ataxia in itself represented only a minor problem in most of the cases and usually improved with age. The additional problems most often represented greater difficulties for the child as well as for its family and should be given great concern in treatment.

The findings indicate the necessity of having a child with ataxia viewed in its entirety from a wide angle by a team of different categories of health personnel. Early diagnosis of defects with detection of maldevelopment and maladjustment permits guidance to be given in time, and troubles to be relieved or even prevented.

35 THE GENETICS OF THE DYSEQUILIBRIUM SYNDROME

G SANNER

From the Department f P ediatrics University Hospital Uppsala Sweden

genealogic and genetic study of 23 patients th the dysequilibrium syndrome (1) is pre- ited.

The birth incidence rate in the two north n public health regions in Sweden was found be 1 per 27 000 births, with heavier con ntration in the central districts of Sweden. Consanguinity between the parents of the tients was detected in four families. In two these families, as well as in two other milies, two siblings had the dysequilibrium ndrome, but otherwise the syndrome could t be traced among the relatives. The birth nk distribution of the affected children did ot differ from what would be expected in a normal population. A geneticostatistical analysis, using Weinberg s sibling method and the a priori method of Apert and Bernstein gave results compatible with an autosomal recessive mode of inheritance.

It is concluded that in patients with a typi cal dysequilibrium syndrome a high risk that the etiological factor is an autosomal recessive inheritance must always be considered.

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36 MYOTONIC DYSTROPHY IN INFANCY AND CHILDHOOD

I GAMSTORP and M VESELINOV

From the Department f Paediatric University f Uppsala, and Department f Paediatrics Centrallasarettet Jönkoping Sweden

he characteristic history and findings in yotonic dystrophy with early onset are

In early infancy (including newborn per iod) severe muscular hypotonia, cyanosis due to inabil ty of the infant to get rid of mucus, weak cry and poor sucking due to weak facial muscles are the typical symptoms and signs. Myotonia is usually not demonstrable by clinical methods. The condition is as a rule misjudged as caused by a supposed cerebral hypoxia.

- In late infancy and early childhood the psychomotor development is slow These children usually learn to sit at about one year of age, to walk after two They remain floppy The cyanotic spells disappear Feeding difficulties are overcome, because the child learns to eat without sucking and thus does not need so much strength in the lip muscles. The facial muscles remain weak and inactive the temporal muscles are atophic, the child s mouth hangs open and drooling becomes a problem. It is usually impossible to demonstrate myotonia by clinical methods. These children are often diagnosed as cases of unspecific mental retardation.

3 In later childhood the mental development remains retarded. The lack of facial movements, the hanging chin the drooling and the delayed development of speech (partly

due to the weakness of the lips) enhance the impression of the severity of the retardation All movements are performed slowly and clumsily Many of the patients have a true muscular weakness, mainly localized to leg muscles, both distal and proximal and the neck muscles. Myotonia can usually be demonstrated by clinical methods. Opacities may be found in the lenses. ECG may reveal evidence of cardiomyopathy These patients are often diagnosed as cases of unspecific mental retardation with speech difficulties and mild cerebral palsy or atypical muscular dystrophy with mental retardation

Myotonia is in all age-groups demonstrable on electromyography No specific treatment for the disease is available.

The family history is often given as non contributory at the first interview The disease is, however inherited as an autosomal dominant. An examination of both parents must be made and as a rule reveals evidence of the disease in one of them. Quite often the diagnosis is immediately apparent, because the affected parent has facial weakness, and myotonia can be felt at the hand-shake· occasionally a thorough examination including electromyography and a slit-lamp examination, is necessary to establish the diagnosis The affected parent is usually unaware tha anything is wrong

A correct diagnosis in the child thus may provoke a family examination leading to th diagnosis in several affected family member all carrying a 50 per cent risk of producing affected children. Myotonic dystrophy wit onset in early childhood is a severe disease usually causing mental retardation cardiomyopathy and muscular weakness, and cor rect genetic information is therefore import ant and may prevent the birth of severel handicapped children.

37 THE PROGNOSIS OF MIGRAINE IN CHILDHOOD

B BILLE

From the Department f Paediatrics University Hospital Uppsala, Sweden

In 1955 the incidence of migraine in about 9 000 schoolchildren in Uppsala was found to be 4 per cent.

In 1957 a group of 73 children with more pronounced migraine was matched in pairs and compared with a control group in which the 73 children had neither migraine nor other frequent headache

In a follow up study in 1961 it was found that 34 per cent had become free from migraine symptoms. In the control group one girl got migraine and four other girls frequent non-migrainous headache. An attempt was also made to assess the value of certain factors in the short term prognosis, but unfortunately with negative results.

In 1971 it was found that out of the 7 children 41 per cent had become free o migraine, 32 per cent had improved and 2 per cent had not improved or had becom worse compared with 1955 Again an attemp was made to assess the value of certain fac tors in the short-term prognosis. For girls o for migraine children with visual aura th prognosis was shown to be unfavourable. I the control group eight children (11 per cent) all girls, had got migraine.

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38 MEDICO-SOCIAL PROGNOSIS FOR CHILD EPILEPTICS

M. SILLANPÄÄ

From the Department of Paediatric, University of Turku, Turku, Finland

The patient series of 245 epileptics below the age of 16 years, from a defined geographic area in South-Western Finland, with defined recurrent epileptic seizures (without demonstrable cause or continuing infection) at the defined period of time and hospitalized for seizures were examined after the minimum follow-up of seven years (mean ten years) for seizures and social prognosis. Adequate control samples were available for certain social aspects.

The average prevalence rate was 3.2 per 1000 and the average annual incidence of epilepsy 0.25 per 1000 in the population aged 0—15 years.

No substantial differences occurred as to sex difference, age at onset, suggested aetiology neurological state, intelligence level or different types of epilepsy classified according to the amplified Final Proposal for Classification of Seizures (Gastaut 1970)

Final remission from seizures is shown in the *Table* No virtual differences existed between different types of epilepsy

Intelligence level was normal (IQ 85) in 47.3 per cent, deficient in 13 1 per cent and gravely to profoundly abnormal in 22 8 per cent of cases. Sixty five per cent of cases had started or completed the Finnish compulsory school system. The main activity of the patients of 16 years or more was as follows: employed 44.6 per cent, school children or students 30.7 per cent, working family members 5.0 per cent and unoccupied 19 8 per cent of cases. All the figures are significantly inferior to those of the average population.

Neurotic disturbances occurred in 55.2 per cent, psychoneurotic in 29.7 and psychotic in 10.8 per cent of cases. One third had hyperkinetic syndrome. Psycho-social adjustment, calculated by the use of different criteria, such as personal independence and capacity for interpersonal contacts, was studied. Forty four per cent of cases were completely independent for age, while 14.2 per cent were slightly to moderately 18 4 per cent greatly and 23 4 per cent completely dependent on other persons

Altogether 29 9 per cent of cases had been institutionalized at least once, mainly however for severe intelligence defect or behavioural disturbances.

Low intelligence level, need for institutional care and high mortality correlated to persistent seizures. No correlation to seizures was, however demonstrable as to school achievement, employability or behavioural disturbances.

Table Final remission from seizures

Never	106 (44.2)
1 year	8 (3.3 %)
1—2 yrs	9 (3.7 %)
2—3	11 (4.6 %)
3—5	23 (9.6 %)
5—7	17 (7.1 %)
7 yrs or more	66 (27.5 %)
Total	240 (100)

39 ELECTROENCEPHALOGRAPHY AND VARIATIONS OF PERSONALITY STRUCTURE IN A NORMAL AND A PSYCHOPATHOLOGIC GROUP OF ADOLESCENTS FROM THE AGE OF 15 THROUGH 21 YEARS

G. BERNLER and O EEG-OLOFSSON

From the Departments of Child Psychiatry and Pediatrics University of Goteborg Sweden

SESSION II B

IMMUNOLOGY AND ALLERGY

CHAIRMAN: ØYSTEIN AAGENÆS

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40 A CASE OF GRAVE CELLULAR (T-CELL) IMMUNODEFICIENCY

P J MOE, S. FRØLAND LS BOTNER nd S. THUNOLD

From the Departments f P ediatrics nd P thology University f Bergen Resear h Instit te of Rheumatology University f Osl nd Department of Paediatric Stavanger Hospital, Norway

Studies in infants with thymic hypoplasia suggest that immunoglobulins can develop in the absence of T-cell function. The purpose of this presentation is to report an infant with grave cellular immunodeficiency associated with a high ratio of B-lymphocytes. This probably represents an intermediate form between the Swiss and Nezelow s type of immunodeficiency

CASE REPORT

S. M. B., a male infant, was admitted to the Depart ment of Paediatrics, Sta anger Hospital, at the age of nine months H w the only child of a 26-yea -old mother N family members ga e evidence of unusual susceptibility to infections. At the age of 8 months, the patient had recurrent fever cough and started to lose weight. Roentgenographic examination revealed extensive lung infiltrations. Antibiotic therapy had no effect and he wa tran ferred to the Children Hospital, University of Bergen, the ge f 10 months. On admission he was in marked respiratory distress, dystrophic and p le with peripheral cyanosis. His general ppearance suggested thymic dysplasia. Neither lymph nodes nor tonsils could be demonstrated.

N defect was demonstrable in the phagocytic func tions of leukocytes. Both in vivo and in vitro studies of T-cell demonstra d deficien func ion The patient was not sensitized by dinitrochlorobenzene (DNCB) and no positive skin reaction was seen f er intrader mal testing w th candida and streptococcal antigens Non-specific mitogens, thought to stimulate T lym phocytes, (PHA, PWM, Con A), did not induce DNA synthesis in blood lymphocytes in vitro. However normal response was seen w th allogeneic, mitomycin C treated lymphocytes in mixed lymphocyte culture (MLC) Only 0.2 / of blood lymphocytes had recep tors for sheep erythrocytes demonstrable with rosette technique (normally 5—35 /)

B-lymphocytes in blood were determined with immunofluorescence technique, utilizing membrane bound Ig marker More than 85 B-lymphocyte were found (normally 3—22 /) with 75 %, 3 /o, and 1 positive for IgM, IgA and IgG respectively Immunoglobulin serum concentrations were: IgG 2. mg/ml, IgM 0.4 mg/ml, and IgA 0.2 mg/ml. N tural antibodies were found in the patient s serum.

Symptomatic therapy was given with o ygen and intra enous fluid. He also received intensi e antibiotic therapy as well as pentamidin. H was all the time in a critical condition. Based on the above laboratory report of gra e cellular (T-cell) immunodeficiency fetal thymus tissue was implanted four times during a one month period.

Eigh days after the first thymus implantation the PHA response was still absent, and the proportion of B-lymphocytes was unchanged, thus gi ing no evidence of maturation of T-cells.

No clinical improvement was seen following the four thymus implantations and the inf t died 24 hours fter the last transplantation.

Autopsy revealed thymic hypoplasia with deficiency f small thymocytes and Hassall's corpuscles. The

parathyroids were present. The bone marrow w s of normal cellularity lymph nodes, Peyer' patches d tonsils were absent and the appendix and spleen showed marked deficiency f small lymphocytes. N plasma cells were detected. The immediate cause f death was giant cell pneumon a.

The mother is now pregnant. Proper precaution will be taken t del ery in order to oid infections until complete immunologic work-up has been per formed in the newborn infant. Therapy must be started as early as possibl in case of immunodeficiency It is too late when the infan is in severe chronic respiratory distress.

Address P J M
Department of Paediatrics,
University of Tromsø
9012 Tromsø, Norway

41 CELLULAR HYPERSENSITIVITY TO RENAL AND INTESTINAL TISSUE IN A FOLLOW UP OF GLOMERULAR DISEASES IN CHILDHOOD

E. NATHAN

From the Children' Hospital F gl bakken C penhagen, Denmark

In 1968 Bendixen (1) reported that the mig ration of leucocytes from patients with active glomerulonephritis was inhibited by renal tissue when examined by a capillary tube migration technique. A similar inhibition was not seen with leucocytes from normal persons or patients with terminal nephropathy or pyelonephritis. In 1970 Rocklin et al. (4) showed that the migration was inhibited by glomerular-basement-membrane (GBM) chief ly in patients with linear IgG deposits on the GBM.

At a 15—25 years follow-up of glomerular diseases in childhood the leucocyte-migration test (LMT) was carried out in 62 persons. Originally 51 had acute glomerulonephritis (GN) 4 had GN without acute onset, 3 had nephrotic syndrome without histologic examination, 2 Schønlein-Henoch nephritis, 2 hereditary nephritis and 1 orthostatic albuminuria. The LMT as described by Bendixen was carried out using both fetal renal tissue and intestinal tissue as antigen. The leucocyte-migration-index (LMI) is the ratio between migration of the test leucocytes in culture with and without antigen. As a control the leucocytes from 59 persons without renal disease were tested using renal tissue as anti gen. The normal range (mean ± 2 S D) of LMI 0 98 ± 0.24

In the follow-up group 14 had abnormal LMI (22.6 /) ? had stimulated migration with both renal and intestinal tissue. With renal tissue 4 had stimulated and 2 had inhi bited LMT Using intestinal tissue 9 had stimulated and 1 inhibited leucocyte migration. There was no significant difference beween the mean in the follow up group and the controls, but the difference in variance was significant on the 5 % level. This was found both with renal and intestinal antigen.

Six of the patients with abnormal LMI had no other signs of disease. 1 had protein and erythrocytes in the urine, 1 had erythrocytes in the urine and a slight but positive antinu clear factor and antihuman-globulin-consum tion test (AGKT) 3 had moderately decreas ed creatinine clearance, had positive AGKT and 1 patient elevated blood pressure. There was no difference between the frequency of abnormal findings in the patients with normal LMI and those with abnormal LMI

Stimulation of the leucocyte migration (LM) is seen when the hypersensitivity is less pronounced and inhibition when it is pronouced. Normal LM is seen when the hyper

sensitivity is of middle degree (5) Some of the patients in the follow up probably had a hypersensitivity of middle degree and their LMI would be normal. The number of abnormal LMI found in the follow-up is therefore a minimum

Hypersensitivity to streptococcal membranes has been found by the LMT in 46 % of cases of chronic proliferative GN (2) Antistreptococcal antisera have a wide range of crossreactivity to cells of several tissues (3) In this material all but one of the patients with abnormal LMI had raised serum antistreptococ titers either originally or at the time of follow-up This may offer an explanation of the high number of abnormal LMI and of the fact that the leucocytes also reacted to intestinal tissue.

Renal biopsy was not performed in any of the patients. Therefore it is not known whether the cellular hypersensitivity was based on active autoimmune processes in the kidneys or not.

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4? THE IMPORTANCE OF GERMFREE ENVIRONMENT FOR THE SEVERITY OF GRAFT VERSUS HOST DISEASE IN BONE MARROW TRANSPLANTED CHILDREN WITH SEVERE COMBINED IMMUNODEFICIENCIES

K HENRIKSEN C. KOCH, F JUHL and K. JENSEN

From the University Clinic for I fectious Diseases the Department of Clinic l Microbiol gy Blegdamshospitalet Copenhagen, Denmark and the C penhagen Study Group f Immunodef ciencies (including also Andersen, V Dupont, B Ernst P Faber V Killmann, S Aa., Muller-Berat N Thomsen, M Svejgaard A Sonderstrup G and Wiik A)

Children with severe combined immunodeficiency syndromes (CID) are extremely susceptible to infections. The decreased resistance becomes greatly enhanced during periods of graft versus host disease that regularly follow bone marrow transplantation, even in histocompatible donor — host combinations. This is due in part to gastrointestinal lesions facilitating absorption of microorganisms. Thus in Solberg & al.s BM transplanted patients with septicaemia, identical organisms were isolated from blood and stool cultures (3) Furthermore, during a GVH there is a persistence of immunodeficiency in spite of the presence of immunologically competent cells (1)

On the other hand gross evidence of GVH in irradiated, BM transplanted mice was rare in germfree environment compared to conventional mice (_) It thus seems that GVH and infection enhance each other and protection of children with CID becomes especially important during attempts to correct the immune defect.

- children with CID have been isolated in our department for periods of 3½ and 15 months respectively The isolation was performed in a slightly modified laboratory laminar air flow bench and they both underwent antibiotic decontamination according to the bacteriological findings. The children were nursed by surgically dressed staff food, medicine and vitamins were sterile Special attention was paid to the provision of vitamins because of the abscence of a normal intestinal flora. Extensive microbiological monitoring was performed to control the regimen.

The first child was a 5½ month old girl receiving BM from the non histocompatible father She had severe diarrhoea necessitating intravenous catheter In spite of a moderate GVH antibiotics were stopped after 2½ months and recontamination attempted with apathogenic bacteria to combat lifethreatening diarrhoea. E. coli rapidly recurred in the stools, and could soon be demonstrated in blood and spinal fluid and she succumbed due to overwhelming infection. This case illustrates the hazard of recontamination during an existing GVH, as previously stressed by Solberg & al. (3)

The second child was ₋½ months old when admitted, he had a purulent otitis growing Pseudomonas aeruginosa and Streptococcus fecalis. After 4 months recurrence of the otitis due to P aeroginosa took place. Only one exogenous microorganism, however contaminated the child during the isolation, a P maltophilia, which was cultured from the mouth and a bowl containing pacifiers.

3 BM transplantations were performed in the child from an HL A non-identical, but M L C identical donor This child experienced only slight symptoms of GVH, which is due probably to a high degree of histocompatibility between donor and host, although the germfree state may have contributed to the mild course.

Besides the selection of a histocompatible donor germfree environment seems to be essential to combat the 2 factors jeopardizing the successful outcome of BM transplantation, GVH and infection.

The regimen described may also be extremely valuable in the treatment of patients with spontaneous or induced marrow aplasia.

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43 STUDIES OF CELLULAR IMMUNITY IN CONGENITAL CYTOMEGALOVIRUS INFECTION

G EMÖDI V MIGGIANO* A. OLAFSSON M. JUST

From the Department of Microbiology and Immunology of the Children Hospital University of Basel, and Basel Institute of Immunology Basel, Switzerland*

About 1.5 % of all newborns excrete cytomegaloviruses in the urine but of 30 children with virus excretion only 1 shows clinical symptoms. The reasons for this are not clear Studies were done concerning the possibility of a defect in the cellular immunity of children with clinical signs of the cytomegalovirus infection

We tested the production of interferon by *lymphocytes and lymphocyte stimulation by* phytohemagglutinin, concavalin A and pock weed. Mixed lymphocyte cultures (MLC) were carried out at the same time.

In children with clinical symptoms of congenital CMV infection (such as hepatosplenomegaly thrombocytopenia mental retardation) interferon production by lymphocytes was found to be significantly reduced and the reactivity in MLC was altered compared to the controls (children of the same age with *and without cytomegalovirus excretion in the* urine but without any clinical symptoms).

No differences were found in PHA pock weed and concavalin A stimulation. The fetus with a disturbed cellular immunity may show signs of disease after cytomegalovirus infection whereas a fetus with a normally functioning immune system may acquire infection without tissue damage.

44 HUMORAL IMMUNITY AND THE COMPLEMENT SYSTEM IN JUVENILE RHEUMATOID ARTHRITIS

H. M. HØYERAAL and O. J. MELLBYE

From the Institute of Immunology and Rheumatology Rikshospitalet Oslo Norway

As children with juvenile rheumatoid arthritis not infrequently have auto-antibodies in their sera, we have studied the immunological apparatus in such patients and in healthy controls. 34 age and sex-matched children in each group were investigated. In sera from the patients rheumatoid factor was found in 21 %, antibody *to the pepsin site of IgG in* 50 % and antinuclear antibodies in 35 % whereas the corresponding percentages for the control group were 3 44 and 0 respectively. Delayed hypersensitivity testing showed that the patient group had a significantly lower reactivity than that of the control group (1).

This presentation includes quantitation of antibody production following antigen stimulation and quantitation of naturally occurring antibodies, immunoglobulins, complement factors and immunoconglutinin. Blood was taken before and 2 weeks after immunization.

There was no significant difference in the antibody production to Brucella by the patient and the control groups. IgM dominated, conforming with a primary response. The secondary response, measured by the reactivity to Diphtheria and Tetanus vaccines, was significantly greater in the patient than in the control group. No significant difference was found with regard to naturally occurring antibodies. *The patient group had significantly* higher serum values of IgG, IgA, IgM total haemolytic complement, C 3, C 4 and immunoconglutinin but no significant difference was found with regard to Clq.

No quantitative defect, rather an increased activity of the humoral part of the immunological apparatus and the complement system, was found in the patient group.

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45 BONE MARROW TRANSPLANTATION IN TWO CHILDREN WITH SEVERE COMBINED IMMUNODEFICIENCY

C. KOCH, K. HENRIKSEN, F. JUHL, V. ANDERSEN, B. DUPONT, V. FABER, K. JENSEN, N. MULLER BERAT, A. SVEJGAARD, F. UTZON

*The Copenhagen Study Group of Immunodeficiencies**
The University Clinic for Infectious Diseases, Blegdamshospital,
Statens Seruminstitut Blood Bank and Department of Clinical Microbiology at Blegdamshospitalet
The University Department of Pediatrics, Gentofte
The University Department of Pediatrics G, Rigshospital, Copenhagen, Denmark

Severe combined immunodeficiency (CID) is characterized functionally by profound depression of humoral and cell mediated immune functions, and clinically by extreme susceptibility to all kinds of infectious agents (1). The disease is invariably fatal within the first, or at most, second year of life. In the last few years about a dozen children with CID have, however, been successfully treated by transplantation of bone marrow (BM) cells. Thus reconstitution of both humoral and cell mediated immune functions has been achieved, leading to prolonged survival and freedom from significant infections (2, 3). In nearly all cases the donor has been an HL A identical sibling, whereas BM transplantation from non histocompatible donors has regularly led to the development of fatal graft versus host (GvH) reactions due to the assault of genetically foreign immunocompetent cells on the child's tissue.

We have undertaken BM transplantation in two children with CID, in neither of whom an HL A identical sibling was available as a fully suitable donor. Detailed reports are to be published (C. Koch et al, in preparation). The first child was a girl, M. K. J, born 21.10.70. In addition to CID she presented some additional features including very severe chronic diarrhoea and a transient period of hypoglycemia. The father was chosen as BM donor and measures were undertaken to circumvent the anticipated GvH reaction by fractionation of the BM cells by the method of Dicke* (4). This led to avoidance of the acute or early GvH reaction, and to some reconstitution of immune functions, but a late or chronic GvH reaction subsequently developed, and during this the child succumbed to overwhelming E. coli septicaemia.

The second child is a boy, K. K. R. J, born 25.7.71. In this case a maternal uncle was chosen as BM donor. He was HL A non identical with the child but his lymphocytes failed to react to the child's lymphocytes in mixed lymphocyte culture (MLC) reactions (5). Three transplantations had to be carried out and although donor lymphocytes were present in the circulation of the child from very shortly after the first transplantation, restoration of immune functions was not adequately achieved until several months after the third transplantation. This child experienced only mild symptoms of GvH in connection with the first transplantation. He was discharged in December 1972 when full restoration of cell mediated immune functions, and partial restoration of humoral immune functions, had apparently been achieved. He has remained in full health till time of writing (February 1973) in normal home surroundings. The course of events in this child indicates

* Including also P. Ernst, S. Aa. Killmann, G. Sandersstrup Hansen, M. Thomsen, A. Wiik.

that the reactivity of the donor's lymphocytes in MLC reactions may be of critical importance for the development of GvH reaction, and gives hope of finding suitable donors for future BM transplantation in cases of CID where an HL A identical sibling is not available. The importance of effective germ free isolation and decontamination will be discussed in a separate presentation.

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46 IGM LATEX TEST AS SCREENING PROCEDURE FOR SERUM IGM LEVELS IN NEWBORNS

K. M LUNDMARK

From the Department of Paediatrics University of Umeå Sweden

47 LONGTERM TREATMENT OF ASTHMATIC CHILDREN WITH SYNTHETIC LONGACTING ACTH (SYNACTHEN DEPOT)

E. OBERGER & I ENGSTRØM

From the Department of Paediatrics, Karolinska sjukhuset Stockholm, Sweden

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SESSION II C

CARDIOLOGY AND ADOLESCENCE

CHAIRMAN: OLAFUR STEPHENSEN

48 TAKAYASU'S ARTERITIS (AORTIC ARCH SYNDROME) ANEMIA AND SKIN RASH IN AN INFANT

P J MOE, K. MAURSETH & E. GLOCK

From the Departments f Paediatrics Radiology and P thol gy University f Bergen Norway

Takayasu s arteritis mainly occurs in Asia and Africa in young adult females. The disease is caused by an inflammatory process in the aorta and its major branches. Symptoms may be due to disturbed blood flow to the brain or hypertension caused by narrowing of the renal artery Occasionally aneurismal dila tation or rupture of the aorta or one of its branches may occur

CASE REPORT

A. S., female, born June 24th, 1969 The disease started at the age of about 1 /2 years with recurrent erythema multiform rash and pyodermia. From bout the same time fall in her hemoglobin to 7.7 g/100 ml at the age of 2 years and persistent leucocytosis were observed. Roentgenographic examination at the ge of 2 years was interpreted as showing mediastinal tumor Rightsided thoracotomy revealed, however only an enlarged thymus; histology showed some eosinophilic changes. Later roentgenograms disclosed pathological contour of the descending aorta. Aortography in M y 1972 revealed marked wall changes and calibe aria tions of the aortic arch and its branches. A systolic murmur was heard at the basis of the heart and in the neck. Blood *pressure has been persistently low* in the arms and high in the legs. The arms have been almost pulseless.

Skin biopsy revealed diffuse lymphocyte infiltration, also around and in the vessel wall.

After the discovery of the aortic arch changes, Prednison, 20 mg, was given daily for a month and the child has in January 1973 been on Prednison, 20 mg every other day for 7 months. She has been in excellent condition with no symptoms from the car diovascular system. There has been no further skin rash, her hemoglobin concentration increased rapidly to normal and she has also otherwise normal hemogram. I the beginning of January 1973 the pulse in her arms was much stronger than previously and the BP in her arms and legs was almost normal. The pathological contour of the descending aorta as seen on chest x-ray picture has remained unchanged.

This is probably the youngest reported case of Takayasu's arteritis and the first case with the triad skin involvement, marked nemia and arteritis. No cardiovascular symptoms have ever been observed in the child, and the arteritis was an incidental finding. Prednison therapy has so f completely prevented further skin rash, has normalized the blood atus and also seems to have prevented recurrent respiratory infections. I is ou hope that long-term use of Prednison also will prevent the progress of her rteritis, as this usually is disastrous disease.

Address P J M.

Department of Paediatrics,
University of Tromsø,
9012 Tromsø, Norway

49 PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA IN INFANCY AND CHILDHOOD

J RAMSOE JACOBSEN L. DAMGARD ANDERSEN F SANDOE, J VIDEBÆK and A. WENNEVOLD

From Queen Louise's Children's Hospital Copenhagen, Medical Department B and Department of Paediatrics G Rigshospitalet Copenhagen and Department of Cardiology and Paediatrics Århus Kommunehospital Århus

In a 1—30 years follow-up study of 73 patients with onset of tachycardia before the age of 15 years 54 were found to have paroxysmal supraventricular tachycardia, PSVT 8 had chronic supraventricular tachycardia and 11 had ventricular tachycardia or fibrillation 28 patients had onset of PSVT in the first year of life, constituting the infant group 18 infants had onset already in the first month 26 patients, the child group had onset between 1 and 14 years of age.

30 patients had the WPW syndrome being equally frequent in the two age groups. 9 patients had additional heart disease

At onset the infants usually presented with symptoms of congestive heart failure which was never the case among the children. Although 5 children had had short syncopes, paroxysms in childhood were usually only accompanied by minor symptoms, palpitations being the most frequent. The difference in circulatory involvement and hence the symptomatology is probably due to the different levels of heart rate In the infants the heart rate was usually above 250 per min., average 275 per min whereas the rate was usually below 250 per min. in children average 211 per min during paroxysms. Despite the severity of symptoms in infants, the diagnosis had not often been made before the admittance to hospital Treatment with digitalis improved the infants markedly as the signs of cardiac failure diminished or subsided, and usually sinusrhythm was restored for shorter or longer periods. Two-thirds of the infants, however had recurrences of tachycardia despite the treatment but failure did not reappear Whether or not digitalis and other antiarrhythmic drugs facilitated the conversion to sinus rhythm could not be established. Vagal stimulation was only rarely effective.

Preventive treatment with digitalis and other antiarrhythmic drugs seemed to have little if any effect on the frequency of recurrences.

The prognosis as to the persistence of the disorder was favourable in the infant group, but not in the child group 23 patients in each age group had been followed for at least 5 years. 17 of the infants and 3 of the children had been without tachycardia for the last 3 years or longer In fact 13 of the 17 infants had their last attack of tachycardia before the age of 6 months. Patients with the WPW syndrome had a somewhat higher incidence of persisting PSVT than those without.

50 PAROXYSMAL TACHYCARDIA IN INFANCY FOLLOW UP STUDY OF 47 SUBJECTS AGED 10 TO 26 YEARS

A. LUNDBERG

Elevmedicinsk avdelingen i gem nd kolan Stockholm

Forty-seven subjects aged 10 to 26 years (33 males and 14 females) with ECG-verified paroxysmal tachycardia during infancy took part in a follow up study when their median age was 14 years.

The incidence of recurrence decreases from 55 % during infancy to 17 % up to 10 years of age a slight increase to 23 % is then observed in adolescence. Children with pre-excitation in the ECG display a slightly higher incidence of recurrence of paroxysmal tachycardia during infancy i e. 65 % compared to 46 % in children without pre-excitation in the ECG This difference is not significant until post infancy ages, when children with pre-excitation have a recurrence rate six times greater than children without pre-excitation.

Apart from the high incidence of pre-excitation, nothing especially abnormal could be observed in children with paroxysms after the age of 10 years as compared to children without late recurrences. No signs of reduced physical working capacity were found in this group

Physical over-exertion is a triggering factor for the paroxysm. However exemption from school physical education and sports should only be practiced exceptionally since only a few attacks per year are observed in the majority of cases and since only minor inconvenience is usually caused on those occasions.

Prophylactic maintenance therapy with digitalis, quinidine and propranolol is characterized by relative inefficacy after infancy On the other hand the isolated paroxysm is well managed by digitalis, propranolol or in most cases, by simple reflex vagal stimulation alone

The results of the study suggested that the prognosis was good in the absence of organic heart disease.

51 PULMONARY VASCULAR RESISTANCE IN INFANTS AND VENTRICULAR SEPTAL DEFECT CALCULATED WITH A THERMODILUTION TECHNIQUE

G HEDVALL and H. ARONSSON

From the Department of Paediatrics University of Gothenburg and Research Laboratory of Medical Electronics Chalmers University of Technology Gothenburg Sweden

The development of the pulmonary vascular resistance in infants and children with VSD has been incompletely understood, mostly because of the difficulties in measuring the pulmonary blood flow The vascular resistance in the lungs is an important factor determining the prognosis and operability of the defect. Therefore we are planning a longitudinal study on infants with VSD and present here the first results of this.

The thermodilution method has been used according to Ganz with double thermistors one measuring the temperature of the injectate in the right atrium, and the other the resulting temperature changes of the blood in the main pulmonary artery In the presence of a left to-right shunt through a VSD this gives a value for the pulmonary blood flow assuming that the shunted and non shunted blood is completely mixed in the right ventricle. The pressures have been measured simultaneously in the left atrium (or pulmonary wedge position) and the main pulmonary artery The cardiac index is used in these calculations, giving a resistance unit which should be below 2 at all ages.

Eight children with VSD have been investigated along these lines. A high resistance (more than 2 U) was found in three of them: a girl aged 6 m died after banding of the pulmonary artery a successful operation on the cardio-pulmonary by pass was performed in a 1 year-old and a girl 3 m is being treated medically In one case the influence on the pulmonary vessels of inhalation of 100 % oxygen was tested The resistance dropped slightly from 2 to 1 7 U in a 1½-year-old boy The other children who were 2—6 years old all had normal resistance values.

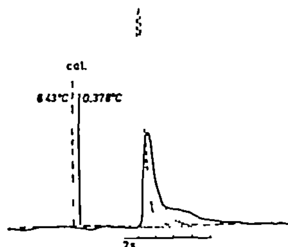


Fig 1 Thermodilution curve from case with small left to-right shunt through a VSD
— — — = injection in right atrium.
———— = dilution of blood in pulmonary artery
= extrapolation of curve for area measurement.

52. ADOLESCENT STRUMA — A FOLLOW UP STUDY

N LUNDSGAARD & J ØSTER

Central Hospital, Randers Denmark

The point of departure for this follow-up study is J E. Mathiasen's classic study of 1962 on the frequency of struma in Randers and the lower part of the Gudenå valley and the subsequent analysis of 43 children, 30 girls and 4 boys, admitted between 1955 and 1961 to the Pediatric Department of Randers Centralsygehus with atoxic struma. All these patients were re-examined in 1962 All patients have now 10 years later been re-examined again.

The patients were called in to the Hospital Anamneses were recorded, and ordinary clinical examinations made Estimations were made of serum-tyroxin, serum-cholesterol, protein-bound iodine, thyroid antigens and serum-creatinine. Four-hour iodine absorptions with iodine 132 were also made Tecnetium-scanning of the thyroid gland was carried out, and a Wasserman glass of serum was frozen for supplementary examination for TSH. An X ray picture of the trachea was also taken.

As the study is not yet completed, the results can not be presented at the present time

53 GROWTH OF THE LUNGS DURING PUBERTY

I ENGSTROM and P KARLBERG

From the Department of Paediatrics Karolinska Sjukhuset Stockholm and Department f Paediatrics, University of Gothenburg, Sweden

Annual measurements of lung volume (vital capacity and forced expiratory one-second volume) were made in approx. 200 children between the ages of 11 and 17 years. The children are the same as those in a prospective longitudinal study of children's growth and development that has been taking place at the children's clinic of Karolinska sjukhuset since 1935 All the data on physical development are now at hand. The lung volume correlates both with the body measurements and the data for puberty development, good correlation being found first and foremost with height, sitting height and the width and depth of the thorax

Significant differences exist between girls and boys and between different age groups in relation to height. A change seems to take place during the period prior to the appearance of puberty This will be elucidated and discussed

54 LONGITUDINAL STUDIES OF BODY COMPOSITION MAXIMAL OXYGEN UPTAKE AND LUNG VOLUMES IN ADOLESCENT BOYS TRAINING FOR BICYCLE RACING

K. BERG and J BJURE

From the Departments f Paediatrics and f Clinical Physiology Barnkliniken, Östra Sjukhuset, and Institute f Clinical Nutrition, Sahlgrenska Sjukhuset Göteborg, Sweden

An initial report on 13 boys, 10.5—14.5 years old, training for bicycle racing has already been presented (1) Since then, nine boys have been studied for 2¹/₂ years and four boys for 3¹/₂ years. Maximal oxygen uptake increased steeply in relation to body weight and body cell mass during the first half year of the study Then there was an increase in absolute amounts but no definite increase in relation to body size. With respect to body composition, body cell mass tended to increase in relation to body weight, body fat tended to decrease and total body water to increase in relation to body weight but not in relation to body cell mass. Total lung volumes and vital capacity increased linearly with maximal oxygen uptake.

Seasonal fluctuations of maximal oxygen uptake and body composition were noticeable in some individuals but not significant for the groups. Data of boys who stopped training after half a year and 2¹/₂ years respectively (and then also refused to participate in the study) did not differ from data of those who continued, which means that lack of motivation must have been their principal reason for stopping.

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55 THE PROPHYLACTIC TREATMENT OF MIGRAINE IN SCHOOL CHILDREN WITH PROPRANOLOL

J LUDVIGSSON

From the Department of Paediatrics University Hospital, Linköping Sweden

SESSION III A

GASTROENTEROLOGY GENETICS AND NEPHROLOGY

CHAIRMAN ROLF ZETTERSTROM

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56 GASTRIC LIPOLYSIS OF HUMAN MILK LIPIDS IN INFANTS WITH PYLORIC STENOSIS

T OLIVECRONA, A. BILLSTROM, B. FREDRIKZON
O JOHNSON and G. SAMUELSON

From the Departments of Physiological Chemistry Anatomy and Paediatrics University of Umeå Sweden

human infants and puppies a suboptimal ncentration of bile acids in the duodenum y interfere with the micelle formation and us with absorption of dietary glycerides. It is erefore of special interest that in 1970 elander and Olivecrona described, in the ckling rat, a lipolytic activity in the stomach. Such an activity has also been found humans but is thought to be of quantitively nor importance in the normal fat digestion the adult. We have found in infants a signi ant hydrolysis of milk triglycerides (TG) to diglycerides (DG) and free fatty acids FA) occurring already in the stomach (Fig). e low pH, the relatively high content of glycerides in the gastric samples and the ture of the disease of these infants suggest at the hydrolysis was not catalyzed by pancreatic enzymes.

A recently discovered lipase present in the man milk was in our experiments inacti ted by heating the milk.

We belive that the pregastric lipase activity n be of great importance in the postnatal gestion of milk triglycerides in the human fant and to some extent compensate for the or bile acid concentration found in these fants.

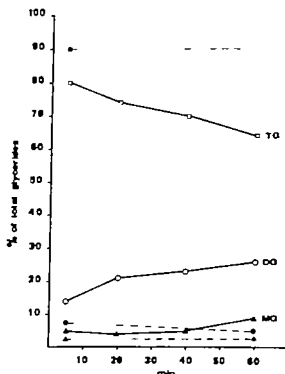


Fig 1 Hydrolysis in vitro of human milk lipids by gastric juice from an infant with pyloric stenosis. The values are expressed in per cent of total glycerides. Filled symbols- heated gastric supernatant. Unfilled symbols — nonheated gastric supernatant.

TG DG and MG stand for triglyceride, diglyceride and monoglyceride respectively

57 LONG-TERM PROGNOSIS IN CHILDREN WITH RECURRENT ABDOMINAL PAINS

M FJORD CHRISTENSEN and O MORTENSEN

From the Department of Paeduatri s University of Aarhus Arhus Denmark

58 USE OF THE NBT TEST AND THE WHITE BLOOD CELL COUNT IN THE PREOPERATIVE DIAGNOSIS OF APPENDICITIS

B. BJÖRKSTEN and L. WAHLBY

From the Departments of Virology and General Surgery University Hospital Umeå, Sweden

Fifty-eight patients who had been operated on following a presumptive diagnosis of appendicitis and four patients, not operated on, with appendiceal abscesses were studied. White blood cell (WBC) counts were performed on 53 of these patients and NBT tests on all of them.

As seen in Fig 1 the WBC count was elevated in most (24/38) of the patients having confirmed appendicitis while the NBT test figures were normal in all but four of them. One patient in this group, with a 21 % NBT score, was febrile on admission but no bacterial infection was noticed Three other patients with appendicitis had moderately elevated (12—16 %) NBT scores as did two patients with no inflammatory signs. No bacterial infection was noticed in these five patients and a second postoperative NBT test was normal Two patients without appendicitis had NBT scores of 21 % and 41 % respectively One of them suffered from diverticulitis sigmoidei and had an elevated ESR. The other patient had no bacterial infection. The four patients having appendiceal abscesses had normal NBT scores although they had ESR of more than 100 mm per hour

The WBC count is apparently of limited value in the differential diagnosis of appendicitis. An elevated figure however strengthens the suspicion of appendicitis. The NBT test seems to be uninfluenced by appendicitis with or without fever and/or elevated ESR. This may be explained if appendicitis is considered as primarily not an infectious, but an inflammatory disease The unresponsiveness of the NBT test to a gangrenous appendicitis is nevertheless surprising

Table 1

Preoperative NBT tests and leukocyte counts on 58 patients operated on with a presumptive diagnosis of appendicitis and four patients with appendiceal abscesses. NBT positive neutrophils are given as a percentage of the total number of neutrophils. The number of white blood cells per cu.mm. of blood is expressed in thousands.

	NBT score %			WBC count		
	≤10	11 19	≥20	<5	5-10	>10
Appendix non-inflamed	9	2	2	2	6	1
Acute nonspecific mesenteric lymphadenitis	6	0	0	2	1	3
Appendicitis	39	3	1	2	12	24
a) acute focal	22	2	0	2	8	11
b) gangrenous and/or perfora ed	13	1	1	0	3	10
) appendiceal abscess	4	0	0	0	1	3
	54	5	3	6	19	28

59 DIAGNOSIS OF CYSTIC FIBROSIS (CF) ANALYSIS OF MECONIUM AND NAIL-CLIPPINGS

H. KOLLBERG K HELLSING and O LANDSTRÖM

From the Departments of Paediatrics and Clinical Chemistry, University Hospital Uppsala and AB Atomenergi Studsvik Sweden

Early diagnosis and treatment are the best ways of improving the outcome of patients with CF Today the diagnosis is mostly based on a sweat test. Since this test is technically difficult, time consuming and only available in a few places, the diagnosis is often confirmed too late Thus, new diagnostic methods are highly desirable.

Meconium from CF patients contains more albumin than meconium from healthy infants (1). Since August 1971 we have carried out a screening programme for CF in newborns based on the analysis of albumin in meconium. A specimen of meconium is collected from the napkin and freezedried, and an aliquot is dissolved. After centrifugation the concentration of albumin in the supernatant is determined by single radial immunodiffusion technique. So far about 5 000 newborn infants have been screened and two cases of CF have been found. In addition meconiums from 23 infants, who have been clinically suspected of CF have been analyzed. The results are given in Table 1

In *nail-clippings* from CF pat[illegible] dium concentration is higher tha[illegible] mal persons (2) We have analy[illegible] pings from 1322 newborn inf[illegible] patients, 22 heterozygotes a[illegible] controls by neutron act[illegible] all CF patients above on[illegible] sodium concentration in the [illegible] lay above 4000 mg/g whereas [illegible] it was lower than 3600 mg/g. The difference in sodium concentration between CF patient and normals seems to be of the same order in nail-clippings as in sweat. During the neonatal period on the other hand, the nails normally also have high concentrations of sodium due to contamination by sodium rich amniotic fluid and therefore analysis of sodium seems to be of little value at this age Heterozygotes cannot be detected by analysis of sodium in nail-clippings.

The two methods are now ready for *clinical use* Detailed instructions for the collection of meconiums and nail-clippings will be given at the meeting (may be requested from

Table 1 *Albumin in meconium (expressed as mg albumin/g dry weight meconium)*

	5 mg/g*		5—20 mg/g**		20 mg/g**	
	Total No.	Thereof CFs	Total No.	Thereof CFs	Total No.	Thereof CF
Screening programme	~5000	0 (?)	16	0	7	2
Clinically suspected	23	0 (?)	2	0	1	7

* In this group only sibs of CF children and children with otherwise strong suspicion of CF have been sweat-tested.
** In these groups all children have been sweat-tested.

H. K.) The department of Clinical Chemistry University Hospital Uppsala, will continue its screening programme for CF with analyses of albumin in meconium. This service is open for all Scandinavian hospitals, which can send meconiums from high risk infants, e. g. sibs of CF children, patients with meconium ileus or patients with other bowel obstructions. AB atomenergi Studsvik Nyköping, has the capacity to analyze nail-clippings for the diagnosing of CF for the whole of Scandinavia (present cost 50 Sw.crowns/analysis)

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60 TRANSIENT COELIAC DISEASE — DOES IT EXIST?

T. LINDBERG and G. MEEUWISSE

From the Department of Paediatrics Malmö General Hospital and University Hospital Lund University of Lund Lund Sweden

By definition coeliac disease denotes a permanent gluten intolerance. Transient coeliac has been discussed in literature but no proof of its existence has been found. About forty children had typical clinical signs of coeliac disease during infancy. They were investigated with xylose and lactose tolerance tests, fecal fat excretion and peroral small intestinal biopsy. The results were in agreement with those found in coeliac disease. The effect of treatment with gluten free diet and also the effect of reintroduction of gluten in the diet was investigated as described above. The mucosa became normal in all the children treated with gluten-free diet. Most of them relapsed clinically and/or histologically when they were given gluten-containing diet. However eight children still have a normal intestinal mucosa after gluten-containing diet for two years. Initially their clinical picture was similar to that of the other children and they reacted favourably to gluten free diet containing cow's milk. It is well known that cow's milk protein intolerance in infancy is transient. It is possible that these eight children might have had a transient gluten intolerance. It is an open question if this condition should be called coeliac disease.

61 FROM THE TRACING AND TREATMENT OF FAMILIAL HYPERCHOLESTEROLEMIA IN CHILDHOOD

G. EG ANDERSEN

From the Neonatal Department University Clinic Rigshospitalet Copenhagen Denmark

Description of lipid pattern in 18 families, in which heart infarct has occurred before the age of 45

Diagnostic considerations in the light of cholesterol and triglycerid screening of 300 newborns.

Dietary treatment of 8 children with pronounced Fredrickson type II hyperbetalipoproteinemia

62 PHENYLKETONURIA, GENETIC ASPECTS

L. WAMBERG and F. GÜTTLER

From The John F. Kennedy Institute, Glostrup, Denmark

Phenylketonuria as a hereditary metabolic disease was first described by Følling (1) in 1934. Early studies by Penrose (5) and Jervis (4) showed that the condition was transmitted by a single autosomal recessive gene with a frequency of approximately 1 in 20 000.

However blood phenylalanine screening programmes among newborns have revealed an unexpectedly high number with Føllings disease, persistent hyperphenylalaninemia and variants. Subsequently the frequency of hyperphenylalaninemia has turned out to be considerably higher: from 1 in 4 000 to 1 in 18 000, depending partly upon the racial and ethnic background of the population being surveyed (3).

Differences in the frequency of hyperphenylalaninemia have also been noticed within the Scandinavian countries and even between the eastern and the western districts of Denmark.

Thanks to biochemical and genetic studies we are now able to distinguish between Føllings disease and other types of hyperphenylalaninemia (2).

From a clinical point of view recognition and differentiation between these conditions is essential for prognosis and for indication and duration of dietary treatment.

According to a recent hypothesis forwarded by Woolf (6) the different types of hyperphenylalaninemia (including Følling's disease) may imply the existence of at least four alleles at the phenylalanine hydroxylase locus, leading to 10 different phenotypes.

Phenylalanine hydroxylase deficiency may be demonstrated directly by measurements of enzyme activity in liver biopsies or indirectly determined on the basis of the amount of tyrosine formed following a phenylalanine loading.

The authors have examined children with Følling's disease and hyperphenylalaninemic children without phenylketonuria as well as their parents, by phenylalanine loading tests. According to their ability to form tyrosine the parents can be divided into three groups: this supports Woolf's suggestion of 3 heterozygote phenotypes.

Our preliminary results suggest that it seems possible to predict the severity of the phenylalanine hydroxylase deficiency in a given child and they may therefore be useful as a basis for genetic counseling.

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63 A FAMILY WITH MOEBIUS SYNDROME

F BECKER-CHRISTENSEN and H. T LUND

From the Department of Paediatrics Copenhagen County Hospital, Glostrup Denmark

The cardinal features of Moebius Syndrome (MS) are congenital palsies of the facial and abducens nerves. (3 4) Various authors have described additional features including affection of other motor cranial nerves, neurosensory hearing-loss, dysfunction of autonomous nerves and a variety of malformations (1 2, 5)

The etiology of MS is unknown About 10 families with more or less characteristic features of the syndrome have been reported (among these ref 1) The pattern of transmission remains obscure.

This study is concerned with a family in some respects different from what has been described previously

Our investigation was initiated by the admittance of a newborn boy with a classic MS When his maternal uncle presented himself with a partial left side facial palsy a closer genetic examination of the family was prompted In a number of family members a partial unilateral lower facial paresis was observed.

The familiar predisposition could be traced back through 4 generations to a common ancestor who died 25 years ago We do not know whether he had a facial palsy himself but he married two unrelated women, and in both marriages he bred offspring who carried the trait. It was possible to establish a pedigree of his descendants comprising 60 persons in 5 generations. In 44 a neurological examination was performed. Only one case of a classic MS was found but in 9 persons an incomplete facial palsy was present.

Besides affection of the 7th nerve other neurological abnormalities were discovered, especially so in a young woman, who was the mother of two children with facial palsy She had no palsy herself but instead of this an affection of the 8th nerves with a symmetric bilateral hearing loss of 80 decibel at frequences above 2000 Herz. In addition she suffered from complete anhidrosis, a complaint she had in common with 6 other members of the family

Ultimately still another feature of MS was observed in a young man, who had a marked tower skull.

Heredity in MS is not unique but this family is remarkable for two reasons. Firstly by the way the mode of transmission is clarified due to the two marriages of the first ancestor and secondly by the scattering of solitary symptoms among at least 15 affected persons

Our findings demonstrate an irregular dominant inheritance of partial features of an old established syndrome.

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64 THE PROGNOSIS FOR GLOMERULAR DISEASE IN CHILDHOOD

E. NATHAN

From The Children Hospital Fuglebakken Copenhagen Denmark

The recovery rate for glomerulonephritis (GN) in childhood found by various authors varies considerably According to Royer et al (4) 50 % were either dead or had some abnormal findings or uremia. Hebert (3) found in his follow-up that all were cured In a follow-up of 239 patients Frisk & Klackenberg (2) examined 95 % of those surviving after 10—20 years and found 5 % with permanent renal damage and 5 % borderline cases. 5 % of the original patients were dead.

104 children with glomerular disease were admitted in 1948—56 to The Children's Hospital Fuglebakken, Copenhagen. By retrospective judgment 81 had acute GN 10 had GN with insidious onset, 2 had hereditary GN 2 Schönlein-Henoch nephritis, 7 nephrotic syndrome without microscopic examination, 1 orthostatic albuminuria and 1 uncertain renal disease. During hospitalization all were treated with antibiotics for varying periods.

At a follow-up 15—25 years later 13 patients were dead and 2 persons could not be found. Of the remaining 89 patients 8 were abroad, 71 (81 %) were questioned and 62 (70 %) were examined. The following analyses were carried out: Hemoglobin, BSR, serum-antistreptococ titers, anti-nuclear factor (ANF) anti-human-globulinconsumption-test (AGKT) complement C'3 C'4 and total-hemolytic-complement, leucocytemigration-test (LT) blood urea, creatinine clearance, Addis sediment count and urine protein analysis.

6 patients had proteinuria, 3 had erythrocyturia and 5 both proteinuria and erythrocyturia. The proteinuria was in all cases of poor selectivity Creatinine clearance was reduced in 15 patients, 7 had high blood pressure and LMT was abnormal in 14 C'4 was low in 1 case and increased in 1 C'3 was increased in 6 cases. The total number of patients with abnormal findings was 39 cases with hyaline casts, serum-antistreptococ titers, AGKT or abnormal complement as isolated abnormalities are not included By clinical judgment 6 patients suffered from chronic GN and in addition 3 were suspected Of these 9 (14.3 %) 7 were thought to have chronic GN at the time of their original discharge, 2 were thought to be cured.

13 of the 104 patients were dead at the follow-up 11 (10.5 %) died as a consequence of the renal disease. 3 died within 6 months of the onset. 2 died ½—2 years after and 6 patients 4—10 years after the onset. The clinical diagnoses were in 3 patients acute GN in 4 patients GN with insidious onset and in 4 nephrosis. Autopsy with microscopic examination of the kidney was performed in 7 4 showed subacute, 1 lobular 1 membrano-proliferative and 1 chronic membranous changes.

There are several problems in comparing the prognosis found in different materials difficulties in controlling the original diagnosis, differences in the selection of the patients, including variance in the percentage of reexamined patients and differences in the tests used at the follow-up Without biopsy it is in addition difficult to know whether the abnormal findings are caused by chronic GN or are a result of healing with a defect In some materials biopsy was performed both originally and at the follow-up but only some of the patients have been followed more than a few years (1 4)

In this material renal biopsy was carried out in 1 patient, 4 have refused and 2 are planned but not yet performed Biopsy has not been proposed to patients with few or slight abnormal findings. Calculation of the true prognosis can therefore not be made on the basis of this material But it is remarkable that 10.5 °/o of the patients were dead in consequence of their renal disease and that only 23 of the 62 examined patients had no abnormal findings 15—25 years after the on set of the glomerular disease.

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65 SERTOLI-CELL-ONLY TESTIS IN CYCLOPHOSPHAMIDE TREATED BOY WITH NEPHROTIC SYNDROME

N E. SKAKKEBÆK, B. PEITERSEN & H. ANDERSEN

From the Children's Hospital Fglebakken and the Chromosome Laboratory Department Y Rigshospitalet Copenhagen, Denmark

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SESSION III B

VARIOUS SUBJECTS

CHAIRMAN: TUOMAS PELTONEN

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66 FLUID THERAPY FOR BURNS IN CHILDREN

T VALKEAKARI

From the Department of Paediatrics University of Oulu Oulu Finland

The requirements for replacement fluid therapy for burns have usually been calculated by the Evans regimen, in other words 2 ml per kg and per cent of burned area for the first post traumatic day and half of that for the second day For estimating the percentage of burned area, Wallace's rule of nine or corresponding empiric tables for children at different ages can be used When using these rules one must always bear in mind the percentages for different parts of the skin. These percentages also vary with the age of the child. The replacement fluid for adults calculated by the Evans regimen does not vary notably For every 10 dm^2 of burned area we can calculate the requirement for replacement fluid to be 1100—1200 ml altogether for 48 hours, regardless of the weight and height of the patient. For children the Evans regimen gives markedly smaller quantities for the same size of the burned area The amounts are always below 1000 ml and for neonates even below 500 ml. According to Cooke losses of fluids are proportional not to the weight or metabolism of the patient, but to the surface area of the second or third degree burn. Therefore, burned areas of equal size always require equal quantities of replacement fluid regardless of the age and size of the patient. If we use 1000 ml as such a common quantity for 10 dm^2 of burn we have a simple rule:

For replacement fluid therapy for 48 hours we need 100 ml per dm^2 of burned area (or 1 cm^3 for every 1 cm^2) One third of the quantity is given in the first eight hours after the accident, the second third in the next 16 hours and the final third during the second day The loss of protein is, according to Bruck, about 1 4 gm for every burned dm^2 To replace this loss, about 40 per cent of the replacement fluid must be plasma protein solution (containing 3.8 per cent plasma protein)

The evaluation of the burned area may be performed in two ways. By multiplying the estimated percentage of burn by the total surface area of the child the area of burn can be directly calculated in dm^2 However it is easier to measure out the burned area directly for instance by means of the doctor's own hand. The flat of the hand without fingers corresponds quite closely to 1 dm^2 in a medium-sized person Both methods must naturally give the same result.

The replacement fluid quantity calculated as mentioned above, will be larger than that given by the Evans regimen However in the Department of Paediatrics in Oulu we have not been able to find any child who would have been hyperhydrated during a period of over one year by means of the former method

67 ACUTE HAEMATOGENOUS OSTEOMYELITIS IN CHILDREN INCREASING FREQUENCY AND CHANGED CLINICAL PICTURE

C. FORSELL

From the Department of Paediatrics Central lasarettet Jönköping, Sweden

Recent years have witnessed an increase in the frequency of osteomyelities in the district of Jönköping besides which several cases have shown a deviating course and localisation It was therefore decided to undertake a retrospective investigation of a 16-year material (1957—1972) During that period 26 cases of osteomyelitis in children (17 boys and 9 girls) below 15 years were cared for at Jönköping Hospital.

Seven children were under 1 year of age, the rest relatively evenly distributed over the agegroup The mean age of 5.5 years agreed well with that reported by other workers. The diagnosis was made on the basis of the clinical picture and (positive) roentgen findings in 22 cases and on the clinical findings and blood cultures in the remaining 4

In 5 cases the disease was due to infection with staphylococcus aureus (penicillin-resistant in 3) in the sixth blood culture gave growth of alpha-streptococci.

The patients delay and the doctors delay were 10 and 8 days, respectively

The main symptoms in decreasing order of importance were decreased function (?6 cases) pain (23 cases) and swelling (18 cases) It should also be mentioned that arthritis had been noted in only 4 cases.

The most important laboratory finding was a raised E. S R. (22 above 15 mm/hour) followed by elevation of temperature (18 above 38 C) electrophoretic changes (which showed signs of acute activity in 15) and a shift to the left of the differential count (in 13 cases)

Of particular interest were 4 cases of vertebral osteomyelitis, all diagnosed after 1969 The diagnosis was delayed on the average, 5 weeks because of the diffuse and atypical clinical pictures, in which neurological findings, abdominal pain and attacks of pain were more prominent than the scanty laboratory findings, besides which the roentgen changes had been insidious and had therefore not been observed until a late stage.

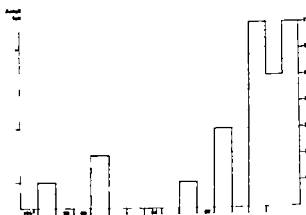


Fig 1 Distribution of osteomyelitis in children during the years 1957—1972 from a district with about 300,000 inhabitants.

Of the 22 cases treated since 1968 treatment in 17 had consisted mainly of lincomycin On the average, the drug was given for 5.5 months and without any noteworthy side effects.

Primary healing occurred in all of the cases without decompression or drainage No complication occurred apart from one slight difference in the length of the legs and one moderate atrophy of the quadriceps.

Acute haematogenous osteomyelitis in children appears to be increasing in frequency and therefore probably deserves wider attention especially since the clinical picture may vary and cause diagnostic difficulties in the early stage This is exemplified in our material by above all the cases of vertebral

osteomyelitis. In this connection it should perhaps be emphasised that repeated roentgen examination is necessary also of the lumbar spine if the patient has symptoms referable to the hips and knees.

If osteomyelitis is clearly suspected, treatment should not be suspended until a firm diagnosis has been obtained, but started immediately. We have obtained good results with conservative treatment, but occasionally biopsy should be done, especially to exclude malignant disease.

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68 THE MODE OF ACTION OF IMPRAMINE AND RELATED DRUGS AND THEIR VALUE IN THE TREATMENT OF DIFFERENT CATEGORIES OF ENURESIS NOCTURNA

K. E. PETERSEN O. ORTVED ANDERSEN and T HANSEN*)

From the Children Hospital F glebakken C penhagen, Denmark
) Biological Laboratories Dumex Ltd. Copenhagen Denmark

The purpose of this investigation was an attempt to elucidate the mode of action of imipramine. The antidepressive effect as well as the anticholinergic effect of the drug might be responsible for the well-documented effect on nocturnal enuresis. Another purpose was to elucidate how to select the children who may derive greatest advantage from treatment with imipramine.

In a double-blind, cross-over clinical trial, imipramine, emepronium (anticholinergic drug), imipramine-N-oxide (same antidepressive effect as imipramine, but no anticholinergic effect) and placebo were administered at random to 69 out-patients suffering from heavy nocturnal enuresis. The children were divided into 4 groups judged by the following criteria: primary/secondary enuresis and with/without attending behaviour disorders. A 50 mg dose (applies to each of the 3 active drugs) was administered for 4 weeks one hour before bedtime irrespective of age and weight. Only a few side-effects were registered, none of them severe.

30 per cent of the children stopped bed wetting after 2 weeks' treatment with Imipramine. Based on the total material, treatment with imipramine reduced the number of wet nights to 55 per cent in comparison with the number of wet nights during the corresponding placebo period.

Following administration of Imipramine N-oxide the frequency of bedwetting was reduced to 74 per cent, whereas the effect of emepronium did not differ from the placebo effect.

The protracted effect of the drugs was considered in the evaluation of the results.

The effect of imipramine was most pronounced in children with presumed psychogenic disorders (secondary enuresis and attending behaviour disorders), the frequency of bedwetting being reduced to 35 per cent of the placebo-effect, whereas the number of wet nights for children with primary enuresis without attending behaviour disorders reduced to 65 per cent of the placebo ...

After 3 months' treatment, the ...

of bedwetting increased slightly the effect of imipramine, however still being very pronounced. In this evaluation due consideration was taken to spontaneous improvement during the period of observation

After discontinued treatment an increased frequency of bedwetting to previous level was recorded

The anticholinergic effect seems to be in significant (and has, so far never been demonstrated) Children with presumed psychogenic disorders suffering from nocturnal enuresis may reap most benefit from short term treatment with imipramine The effect of the drug on the sleep-level may play an essential rôle, but this was not investigated in the present trial neither was the effect of long term treatment evaluated

69 ABSORPTION AND ELIMINATION OF PHENOBARBITAL STUDIED BY PLASMA CONCENTRATION ANALYSES IN NEWBORN INFANTS AND YOUNG CHILDREN

B. JALLING L. O BOREUS, N KALLBERG and S. AGURELL

From the Departments f Paediatrics and Cl nical Pharmacology K rolinsk jukhuset and the Cent al Military Pharmacy Stockholm, Sweden

70 A STUDY OF THE IMPORTANCE OF A JAPANESE BABY CARRIER FOR THE COMMUNICATIVE DEVELOPMENT OF INFANTS

K. BRZOKOUPIL, U FOHRER, J LIND and K. STENSLAND-JUNKER

From the Department f P ediatrics Karolinska Sjukhuset Stockholm Sweden and Lekot ket på Blockhusudden Stockholm Sweden

A long cherished superstitious belief in physical hygiene and fixed hours for sleep and meals based on unproved premises has led to an ever widening distances between children and parents. The socio-economical structure of Western society has broadened this gap further still Contemporary psychological research believes in the importance of closer physical contact between parents and children as a valuable means of stimulating emoti nal and communicative deve opment There is probably great knowledge to be drawn from cultures where it is part of the normal upbringing of children to carry one s babies while performing one s daily tasks. A systematic study of how Swedish parents — with and without previous experience of infants of their own — feel about using a Japanese baby carrier is going on in Stockholm. The purpose s to ascertain whether this form of physical c ntact can promote the child s social and ental development.

71 HOW DOES YOUR POISON-CUPBOARD LOOK?

K. BRZOKOUPIL and E. JOSEFSSON

From the Department of Paediatrics, Karolinska Sjukhuset, Stockholm, Sweden, and The Swedish Poison Information Center, Karolinska Sjukhuset, Stockholm, Sweden

72. LACK OF ENTEROCHROMAFFIN CELLS IN THE STOMACH OF A CASE WITH CONGENITAL INTRINSIC FACTOR DEFICIENCY

C. FORSELL, J. KUBISTA, B. LINDBLAD, K. LINDSTRAND, G. MEEUWISSE and F. SUNDLER

From the Department of Paediatrics, Jönköping Hospital, Jönköping, the Department of Clinical Chemistry, University of Gothenburg, Gothenburg, and the Departments of Medicine, Paediatrics and Histology, University of Lund, Lund, Sweden

Congenital lack of intrinsic factor has been described in 33 patients including 3 cases from Scandinavia (1—4). We describe the first case from Sweden, a boy born in 1969. Apart from frequent upper respiratory infections during the first year of life no remarkable findings were noted until the age of 2 6/12 years when he was admitted to hospital because of intractable diarrhea for the last month. Physical examination revealed a thin and pale child with glossy tongue and brownish pigmentations around the tips of the fingers and on the genitalia where also an intermittent hydrocele was found. The hemoglobin concentration fell during the following 6 weeks from 10.2 to 5.8 g/100 ml. Bone marrow examination revealed megaloblastic changes, serum vitamin B 12 was below 20 ng/l but serum folate was normal (6.7 ng/ml). Total LDH was 180 E (normal 15—40 E) and thermostable LDH was 160 E (normal 6—20 E). Methylmalonic acid excretion was 220—270 mg/24 hours (normal $<$ 1.2 mg/24 hours).

A Schilling test performed without hog intrinsic factor concentrate showed almost no excretion of isotope (0.2 %) but when repeated together with hog intrinsic-factor concentrate 5.9 % of the isotope was found in urine. The pentagastrin test showed a normal amount of hydrochloric acid in gastric juice (6.3 mmol/hour). Intrinsic factor in gastric juice could not be detected by a radioimmunologic assay and no vitamin B 12 binding protein with a molecular size similar to human intrinsic factor was found. Gastric parietal-cell and intrinsic-factor antibodies were not detected in serum.

Parenteral treatment with vitamin B 12 resulted in a rapid clinical improvement and a bone marrow aspirate showed no megaloblastic changes, the hemoglobin concentration rose to 11.5 g/100 ml and the urinary methylmalonic acid excretion decreased to 1.0—1.6 mg/24 hours. After 8 weeks of therapy with vitamin B 12 biopsies of the small intestine were normal but a gastric biopsy from

the corpus showed no evidence of enterochromaffin cells although otherwise normal when examined by light and electron microscopy

Investigations of the parents showed normal serum vitamin B 12 (325 290 ng/l and serum folate values (5 8 5 4 ng/ml) normal excretion of methylmalonic acid (2 1 6 mg/24 hours) and a normal concentration of intrinsic factor in gastric juice after pentagastrin stimulation (59 48 ng units/ml)

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SESSION III C

VARIOUS SUBJECTS

CHAIRMAN: BJORN JULIUSSON

73 SUDDEN UNEXPECTED DEATH (SUD)

A. LANSIMIES, S. JAYKKA and T. PELTONEN

From the Children Hospital University of Turku Finland

After the first weeks of extrauterine life infant mortality decreases significantly. However during the 11 months following the first month many unexpected, sudden deaths occur. These deaths have been observed all over the world and great efforts have been made to solve this problem, usually called SUD-syndrome. Some common features can be drawn from these reports. Boys are in the majority in most studies. After the sixth month of life SUD-cases are rare. Other possible causal factors (diurnal and seasonal rhythms, social status, etc.) vary from study to study. No previous studies on SUD-infants have been published in Finland.

Our material was collected with the aid of the State Statistical Bureau and consisted of 124 SUD-cases registered during six years (1963—1968). Infants less than one month of age were excluded. The information was collected from death-registers and, when available, from patient files in hospitals. A careful analysis of all 15 cases from the area of Turku University Children's Hospital (south-west Finland) was performed with re-analyses of histological sections etc.

Relation between sexes was about the same in both materials (m/f) 88/44 and 11/4 respectively. 83 % of SUD-cases occurred before the age of seven month. Annual variation was between 12 and 23 cases. No increasing or decreasing tendency was observed. Seasonal variations were statistically non-significant. Urban/rural relation was the same as in the whole population. A slight tendency towards over representation of lower socio-economic groups was observed. The correlation cannot, however be considered as significant, because of the lack of statistics for Finnish children. Correlations could thus be drawn with the adult population only.

The causes of death were determined by a large number of physicians and might be inexact. However suffocation was the cause of death in 58 % of 124 cases, 34 % were considered as aspirations and others were various infections. In the subgroup of 15 cases (13 % of all cases) 13 were suffocations, two of them had microscopically detected respiratory infection. Two had macroscopically clearcut lung inflammation with atelectasis. No other features of importance were observed macroscopically or microscopically. According to our study Finnish SUD-cases did not show any national special signs nor did our study reveal any possible causal factors. The problem of SUD in infancy can probably only be solved after prospective study of a rather large population.

74 THE FIELD OF ACTIVITY OF SOCIAL PAEDIATRICS

S. HEINILD

From the Department of Social Paediatrics Rigshospitalet Copenhagen, Denmark

Social paediatrics is defined as the field of medical science that is devoted to the study of the influence of the social environment on the development of diseases during childhood and the treatment of these diseases. Indeed social paediatrics is not a modern invention and it is definitely not a sub-speciality On the contrary it is a principle by which it is aimed to open up a topical, though not historically novel vast and mainly stagnating field of research.

It is first explained why the changed social circumstances call for a revision of the relations between medical practitioners and patients. Quite a few of the pathological conditions to be encountered in the modern highly industrialized society of our day do not come within the sphere of a medical science which exclusively relies on biology and natural science, owing to the fact that differentiation between the so-called diseases and social adaptation difficulties is intricate The medico-scientific view of the two elements deviant behaviour and morbid behaviour can hardly escape being influenced by the prevailing social and cultural standards which have been adopted, or which may have given rise to reactions, even though they under any circumstances, determine the perception and behaviour pattern of patients and physicians.

The conventional structure of the universities, and the limitations of this channel of education has failed to keep pace with the demands and requirements of the surrounding dynamic, evolutionary society Education has to be more socially oriented in the future and the idea of a medical science exempt of value criteria has to be abandoned

The Social Paediatric Outpatients Department in Rigshospitalet (University Clinic) and the attached department in the Seaside Sanatorium at Refsnæs have been working for fi[ve] years under the influence of these points [of] view always in intimate contact with th[e] various sectors under the social authorities a[nd] the public health authorities The experien[ce] thus gained is reported. For one thing, th[e] hitherto practiced one-dimensional system o[f] diagnostics has been found to fail whenev[er] it is faced with matters of a social or paedago[gi]gic character A diagnosis based exclusivel[y] on a biological, physico-chemical nosograph[y] cannot describe a social paediatric clientel[e]. Consequently a new system of diagnosis [is] presented

According to the new diagnostic system the following four factors are included i[n] descriptions of the individual patients

- I *Constitution* (the permanent, indiv[i]dual factors which may be genetic o[r] acquired, for instance defective in[]telligence, cerebral affection).
- II *Environment* (the actual, oecologic[al] conditions, for instance· dwelling economics)
- III *Provoking factors* (unspecific, tempo[]rary deviations from the normal en[]vironment, for instance· divorced pa[]rents, change of school)
- IV *Specific factors* (factors determinin[g] specific, nosological characteristic[s] for instance streptococcal infectio[n] avitaminosis)

The introduction of this diagnostic system will permit the overall situation of the patien[t] to be taken into consideration This may exe[rt] some influence on the therapeutic procedure the scope of which usually also will apply t[o] cases other than the patient concerned.

Accordingly the essential principles withi[n] the field of social paediatrics will be [as] follows

raining of professional staff and instruction of the population at large in order that they may recognize the concept of diseases.

Accentuation of the fact that the vast slope of the biological curve of variations is of biological medical and humanitarian significance.

It shall always be the task of the physician, even his duty to contribute to an improvement of the material conditions of the population.

The lack of faith in psychotherapeutic results must never lead to therapeutic nihilism. So far the possibilities of social treatment still remain to be considered from a medico-scientific point of view.

It can hardly be doubted that ideas on service and relief will steadily progress in years to come. Much misunderstanding and many accidents may be avoided if hospitals, rest homes, sanatoriums and camps are gradually recognized under this aspect and if all concerned can avoid being spellbound — occasionally even obsessed — by the ancient prerogative of medical science treatment of the individual patient.

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75 SOMATOMEDIN AND ITS RELATIONSHIP TO GROWTH HORMONE AND INSULIN IN SERUM IN CHILDREN WITH VARIOUS FORMS OF GROWTH RETARDATION

K. W KASTRUP H. ANDERSEN and K. HANSSEN

From the Children Hospital Fuglebakken Copenhagen

Somatomedin (SM) is generally accepted as a growth hormone (GH) dependent factor in serum. It was therefore found of interest to study its occurrence in various types of growth retardation. Previous reports have dealt with fasting values only. We therefore felt it of interest also to follow the variations in SM during insulin tolerance test, and after injection of human growth hormone. In addition serum insulin determinations were made in most of the patients during these conditions.

SM was measured in serum according to the methods of Hall with some modifications, using embryonic chick cartilage.

The growth-retarded patients were divided into three groups according to their GH response to insulin induced hypoglycaemia. The first group had a normal and the second group a subnormal (Hypopituitary) response. The third group is represented by one patient with *dwarfism of Laron's type: Growth retardation and high immunoreactive growth hormone in serum.*

The results can be summarized as follows:

Fasting SM was normal in patients with normal GH and subnormal in the other two groups. During insulin tolerance test SM response was normal in patients with normal GH, subnormal in patients with subnormal GH response and very low in the patients of Laron s type. Finally the rise in serum insulin after injection of 2 mg HGH was found to be lower than normal in growth retarded patients with low serum GH. In contrast, no rise in serum insulin concentration could be detected in the Laron type patient. This finding has not been previously reported and raises questions of diagnostic and physiologic importance

76 IMMUNOREACTIVE GROWTH HORMONE IN URINE OF CHILDREN AND IN PATIENTS WITH HYPOPITUITARISM AND OTHER FORMS OF GROWTH RETARDATION

K F HANSSEN H. ANDERSEN & K. W KASTRUP

From the Child en Hospital F gl bakken & Steno Memorial H spital, Copenhagen Denmark

Measurement of plasma growth hormone during stimulation tests has added much information to our knowledge of growth hormone in children However the rapidly changing blood levels of growth hormone during 24 hours make it difficult to estimate the secretion rate and elimination of the hormone. It would therefore be of interest to measure the urinary excretion of immunoreactive growth hormone (IRHGH) This measurement has presented difficulties that now have been overcome (Hanssen, K.F Acta Endocr) 71 (1972) 665) With this method we have investigated the excretion of IRHGH in urine in normal children and in children with different disorders of growth. This last group of children was furthermore investigated by measuring plasma growth hormone during insulin induced hypoglycemia

RESULTS

1 Urinary IRHGH increased with chronological age in both normal and growth retarded children
2. Urinary IRHGH was well correlated to body surface in both normal and growth retarded children
3 A positive correlation was shown between urinary IRHGH and the integrated plasma IRHGH response during insulin-induced hypoglycemia in growth-retarded children
4 With a few exceptions, no difference in urinary IRHGH/m^2 between normal children and children with non pituitary growth retardation was shown
5 Hypopituitary children excreted significantly less IRHGH in urine pr m^2 than normal children and children with non-pituitary growth retardation
6 A patient with the syndrome of nanismus with high immunoreactive growth hormone (Laron) had excessively increased urinary growth hormone together with increased plasma growth hormone.
7 A growth retarded patient with proximal renal tubular defect and glucosuria excreted 100 × the normal amount of urinary IRHGH although he had normal plasma IRHGH response to insulin induced hypoglycemia. This confirms the observation that most of the growth hormone present in the ultrafiltrate under normal circumstances is reabsorbed in the proximal renal tubulus and not excreted in the urine.

77 LONG-TERM PROGNOSIS IN CHILDREN WITH URINARY TRACT INFECTION PARTICULARLY WITH RESPECT TO THE DEVELOPMENT OF POST INFECTION SCAR TISSUE IN THE KIDENYS

T BERGSTRÖM

From the Department of Paediatric University of Gothenburg Sweden

78 INSULIN SECRETION AND CELLULARITY OF ADIPOSE TISSUE IN CHILDHOOD OBESITY

A. HÄGER

From the Department of Paediatrics University Hospital, Linköping Sweden

79 WHAT IS THE PURPOSE OF THE EMERGENCY UNITS OF CHILDREN HOSPITALS? PATIENTS' DATA FROM THE KAROLINSKA SJUKHUSET AND S:T GÖRAN SJUKHUS

B. LAGERKVIST

Department of Paediatrics, S:t Göran Hospital and Karolinska Hospital Stockholm, Sweden

SCIENTIFIC EXHIBITIONS

1 INHALATION OF SALBUTAMOL 0.5 % AQUEOUS SOLUTION IN THE TREATMENT OF ACUTE ASTHMATIC ATTACKS IN CHILDREN

T BERG

From the Department of Paediatrics Central Hospital Västerås Sweden

In recent years Salbutamol (Ventoline, Glaxo) administered by a dosage aerosol has been found effective in the treatment of asthmatic attacks. Salbutamol has a selective β_2-stimulating effect. In pronounced asthmatic attacks, especially in children, inhalation from a dosage aerosol may be difficult to manage and therefore ineffective In adults, inhalation of doses considerably higher than those obtained with a dosage aerosol has been tolerated very well Thus the inhalation of 10 mg salbutamol repeated 3—4 times daily has been given without any side effects. It has therefore been considered to be of great interest to study the effect of inhalation treatment with nebulized salbutamol solution in high doses in children with asthma

On 98 occasions 22 children with acute asthmatic attacks were given inhalation treatment with salbutamol in a dose of 0 15 mg per kg body weight. Before starting the inhalation therapy most of the patients had received 1—2 injections of adrenaline subcutaneously with an unsatisfactory effect on their bronchial obstruction. In spite of the high doses of salbutamol no side-effects were noted. Thus the heart rate and blood pressure were not affected appreciably All patients had normal ECGs Peak expiratory flow could be studied on 84 of the occasions when salbutamol was inhaled About 10 minutes after the start of treatment the mean PEF values were nearly doubled. In addition good therapeutic results were found on several occasions even though the patient could not manage to produce a PEF value following inhalation. Thus the therapeutic effect was found to be very good and inhalation treatment with nebulized salbutamol solution in a considerably higher dose than that obtained with a conventional dosage aerosol seems to be a valuable therapeutic alternative in acute asthmatic attacks in children, not least in outpatient care.

2 I HIPPURAN RENOGRAHY IN THE NEWBORN LAMB

L. HALKOLA, L. HIRVONEN E. LANSIMIES and T PELTONEN

From the Cardiorespiratory Research Unit University of Turku and the Department of Physiology University of Oulu Finland

In the foetus a parenchymal organ, e.g. kidney may functionally be in a dormant state (1—4). This corresponds to a relatively low regional blood flow A rapid change and re-

distribution of the blood circulation at birth does not necessarily indicate a parallel change in the function of the organ

Twenty-one renographies on eight newborn lambs (4 hrs to 7 days) were performed with 131 I Hippuran and Wallac-device (Turku, Finland)

The first phase of the renogram, the rapid rise, was observed in all cases. During the first day after birth this was followed by a plateau indicating an insufficient filtration and excretion In the second day of extrauterine life only a slow decline in the activity was recorded after the initial rise. An adult type of renogram was a regular finding from the third day onwards.

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3 GROWTH CHARTS FOR HEIGHT WEIGHT AND HEAD CIRCUMFERENCE

P KARLBERG I ENGSTRÖM, G KLACKENBERG I KLACKENBERG-LARSSON H. LICHTENSTEIN I SVENNBERG and J TARANGER

Department of Paediatrics, University of Gothenburg & Department of Paediatrics, Karolinska Institutet Stockholm

As a part of a prospective longitudinal study of growth and development of 212 Swedish children, growth charts for height, weight and head circumference have been constructed. Since the youngest children in the study were born in 1958 the analysis of the measurements has only been performed up to the age of 13 years. From the age of 13—18 years an older Swedish study by Broman Dahlberg Lichtenstein has been used. As the curves have not been smoothed out, there are breaks in the curves at the age of 13

The charts comprise the period from birth up to the age of 18 years. The growth of height and weight has been followed during the whole period, while the growth of head circumference can be evaluated up to about five years of age Separate charts are used for boys and girls There are two charts for each sex. The first one goes from birth up to the age of eight years. The second goes from the age of 6—18 years.

The charts Birth — 8 years also indicate the points of time when some psycho-motor abilities are developed. The values have been obtained from the same group of children as the somatic measurements. For each psycho-motor ability the points of time corresponding to — 1 SD and + 1 SD has been indicated on the charts.

The charts 6—18 years also indicate the appearing times of puberty ratings according to Tanner Since the youngest children in our study are only 14 years old, we have used the values from an English study by Marshall Tanner A preliminary analysis of the puberty development in our study has shown that there are no great differences in comparison with the English study For each puberty rating the points of time corresponding to $\pm$ 1 SD and $\pm$ 2 SD have been indicated.

4 LEG AND ARM ERGOMETRY IN CHILDREN OF 12 TO 13 YEARS OF AGE

M. MAKARAINEN T PELTONEN and L HIRVO

From the Department of Physiology University of Oulu Finland

s a part of a study on physical fitness of chil ren (normal and dystonic) comparative ergo- etric measurements were made on 14 boys nd nine girls. Three types of experiments were performed until exhaustion: Intermedi ry bicycle ergometer test where the load was ncreased 75 kpm/min with intervals of one minute. With Werding ergometer (Ergomat, W J Werding, Lausanne) separate leg and rm exercise tests in sitting position increase of load on brakes of both sides was 2 kg once a minute. The degree of exertion was assessed with Borg's rating scale modified by Arstila.

Maximum heart rate in the various tests was equal for both sexes. When the bicycle ergometer was used it was 188 ± 7.5 (S.D.) In Ergomat tests it was 156 ± 17 when the work was done with legs and 150 ± 17 when it was carried out with arms. Maximum systolic blood pressure during bicycle ergometer and Ergomat leg tests was 177 for the boys and 161 to 164 for the girls. The difference was not significant. Total amount of work done by the girls was about 60 per cent of that performed by the boys when the legs were used. In the arm exercises sex differences in the total work were insignificant. The total work carried out with arms was on an average 10 per cent of that done with legs.

The results obtained with the two types of ergometers used are not quite comparable. Standardisation of experimental conditions is more difficult with the Ergomat.

5 HOMOCYSTINURIA; THE FIRST RECOGNIZED CASE IN FINLAND

R. NORIO and L. WESTERLUND

From the Research Department, Rinnekoti Institution for the Mentally Retarded Helsinki
Seinäjoki Central Hospital Seinäjoki
Children's Hospital University of Helsinki
Children's Hospital, University of Turku Finland

Due to the exceptional population structure of Finland many rare recessive diseases appear there in excess, whereas some others are absent or occur very seldom. We will now present the first recognized case of homocystinuria. The female patient, 8 years old, whose disease had earlier been diagnosed as rickets and later as Marfan's syndrome, showed mild mental retardation (I Q 62), downward subluxation of the eye lenses and iridodonesis, flushed cheeks, reticularly mottled skin and skeletal abnor... breast, prominent lower ... lumbar lordosis, lumpish ... gum, irregularly aligned ... porotic thoracic an... X ray). The urinary ... was 1.039 mmol/... tion 0.114 umol/ml ...

The parents ... moved and ... area in Central ...

6 A METHOD TO DETERMINE CHANGES IN BODY TEMPERATURE

T PELTONEN P ESKELINEN and E. ERÄKANGAS

From the Cardiorespiratory Research Unit of Turku University Turku
Department of Electrical Engineering, Oulu University Oulu
and the Development Group of Lääketehdas Oy Helsinki

There are few objective methods to determine the status of neonates. Even the Apgar system has been widely criticized (1). To observe the changes in the neonatal skin temperature and their ratio to the rectal temperature has proved to be a satisfactory method (2) To develop an inexpensive and handy instrument our research unit has been working in cooperation with certain laboratories of the Oulu and Turku Universities and with the Development Group of Lääketukku Oy A pocket size digital electrical thermometer has been developed.

SPECIFICATIONS

Measuring range 15 —50°C
Accuracy better than 0.1°C
Measuring time under normal conditions less than 5 sec
Measuring point Ø < 0.5 mm
Digital display
Internal measuring cycle 0.66 s or shorter by special order
Locking of the display for read-out
Disposable cover for rectal measurements
Battery and mains operation
Uninterrupted operation time min. 2 h, recharging time 10 h
Weight 900 g
Dimensions 160 mm × 95 mm × 50 mm, length of probe connecting cable 1200 mm

Considerable saving can be achieved by replacing the expensive Thermovision in certain studies by this instrument. (3 4)

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7 A METHOD FOR ESTIMATION OF SKELETAL MATURITY

J TARANGER, P KARLBERG H. LICHTENSTEIN and B. BRUNING

Department of Paediatrics University of Gothenburg, and Department of Paediatrics Karolinska Institutet Stockholm

As a part of a prospective longitudinal study of growth and development of 212 Swedish children a method for estimation of skeletal maturity has been worked out. Skeletal development of the hand and wrist is evaluated by means of bone stages according to Tanner Whitehouse. Mean appearing time of each bone stage is calculated by probits analysis. Since growth begins at conception we use the logarithm of the conceptional age as time

unit. Each bone stage is then given a maturity value with the exception of the *first* and *last* stage of each bone because no point of time for the beginning respectively the end of these stages can be defined The maturity values of the various bones are then weighed together to an overall skeletal maturity

The assessment of the roentgenograms is made by a visual comparison of the bones with standard figures of the bones stages. The figures have been copied from statistically representative roentgenograms of the 212 children. We have also compiled a revised version in Swedish of the criterias of the various bone stages according to Tanner Whitehouse.

A skeletal profile chart has been constructed by plotting of the mean appearing times of the bone stages. The various stages of each bone are placed in a horizonal row and the different rows are placed under each other If the present bone stages of a child are marked on the chart, a skeletal profile will be seen. The skeletal profile can be used as an aid at the visual assessment (e.g. to make another assessment of diverging bone stages) and at the clinical evaluation (different diseases may have different skeletal profiles)

Since the youngest children in our study were born in 1958, the assessment of roentgenograms has so far been made up to the age of 13 years. Therefore our method can be used only up to the age of about 10 years.

A logarithmic time scale has been used. Since growth begins at conception the logarithm of the conceptional age has been used as time unit. A logarithmic scale has also been used for the different somatic measurements. The biological reasons for using logarithmic scales will not be discussed in this paper There are practical advantages too, since logarithmic scales give more space to the first years, when growth and development are evaluated more frequently than during later years.

The variability of the somatic measurements can be described by different statistical methods, e.g centiles or standard deviations. If repeated measurements of one individual are available, the growth can best be analyzed by standard deviations. When analyzing the growth of individuals with grossly deviating values (3rd centile or 97th centile) centiles are not suitable. Therefore we have used standard deviations as a measure of the variability in our growth charts. When calculating the variability of length-height and head circumference numerical values have been used, while a logarithmic transformation has been used for weight depending on its skew distribution.

8 REPEATED ATTACKS OF CARDIAC ARREST CAUSED BY THE INNOMINATE ARTERY COMPRESSING THE TRACHEA

P VILKKI A. NUUTILA and H. PUHAKKA

From the Department of Paediatrics University of Turku, Turku, Finland

A noisy respiration and dyspnea aggravated by feeding of the infant is known to be caused by the innominate artery compressing the trachea and can be treated by suspending the vessel to the sternum. (1 2, 3) The trachea may be otherwise normal, although in our own cases the babies in question have been operated on as newborns for an oesophageal atresia and a tracheo-oesophageal fistula. One of our cases deserves a special description

as he had only a slight dyspnea but the condition manifested itself by repeated attacks of cardiac arrest.

Case history A male newborn birth weight 2700 g, was admitted for attacks of respiratory distress. An oesophageal atresia and a tracheo-oesophageal fistula were diagnosed and thought to be the cause of the attacks. The fistula was closed and the oesophagus reconstructed by primary anastomosis. The boy made an uneventful recovery with somewhat noisy respiration During the 2nd month of life the baby began to get attacks of cyanosis and bradycardia especially after feeding The noisy respiration stopped and the baby had apnoe and lost consciousness. These episodes occurred from one to ten times a month, the baby needing about one hundred resuscitations during his first 18 months. The ECG-recording during an attack showed sinusbradycardia and an increasing number of ventricular extrasystoles ending in ventricular fibrillation The sinus tachycardia was also seen in all ECG-recordings taken during feeding the baby A provocation by a balloon catheter in the oesophagus slightly above the level of the bifurcation of the trachea produced similiar ECG signs. Between the attacks there were some ventricular extrasystoles in ECG too, but the baby did well At the age of 9 months a tracheal diverticulum was diagnosed and operated at the site of the closed fistula. Otherwise the trachea was normal in structure No improvement was observed after the operation. However in spite of the attacks the physical and mental development was normal. At the age of 20 months the typical view for a compressing innominate artery was seen in bronchoscopy In the operation the thymus (32 g) was removed and vessel suspended to the sternum A simultaneous relief of the compression was confirmed in bronchoscopy The recovery was uneventful no more attacks occurred and the boy could for the first time in his life be safely treated by his parents at home

In light of the case it is obvious that a normal innominate artery at least in connection with a large thymus and previously diseased trachea (tracheomalacia) can exert a compression on the trachea causing, probably by vagal reflexes, attacks of cardiac arrhythmias. Independently of the primary pathology the anterioposterior tracheal collapse can be alleviated by suspending the aortic branches to the sternum

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9 AN IMPROVED MODEL OF CRY DETECTOR REAL TIME ANALYSIS OF CRY RESPIRATORY AND HEART RATES IN THE NEWBORN INFANT

V VUORENKOSKI M KAUNISTO P TJERNLUND and L. VUORENKOSKI

From Dept of Speech Communication, Royal Institute of Technology (KTH), Stockholm Sweden and Dept of Paediatrics Keski-Pohjanmaa Central Hospital, Kokkola Finland

The inconvenience of the sound spectrographic methods for clinical cry analysis has resulted in the construction of a specific cry analyser (2) Both the practical pediatric knowledge and the experimental studies (1 4) indicated the use of three cry parameters —

quantity pitch and duration — in direct, real time detection (3) Routine clinical use of CRY DETECTOR later evoked the desire of measuring the heart and respiratory rates simultaneously with the cry parameters.

The set-up of the present equipment consists of an analyser* and a strip printer (FACIT 4552) The analyser contains 6 cumulative counters for·

- number of cries with a pitch under 1000 Hz (channel 1)
- number of cries with a pitch above 1000 Hz (channel 2)
- total duration of cries with a pitch under 1000 Hz (channel 3)
- total duration of cries with a pitch above 1000 Hz (channel 4)
- number of heart beats (channel 5)
- number of respirations (channel 6)

For recording the cry signal a specially developed contact mike, attached to the skin of the upper chest of the infant, is used The heart and respiratory rates are recorded by means of two chest electrodes. For real time visual reading of the data the positions of the counters, the actual time and the time when the analysis was started may be presented on a digital display The printer records the measured data on pressure sensitive tape automatically with pre-set intervals or by manual operation.

The data obtained from the preliminary analysis indicate the suitability of the method for both short and long-term monitoring of the newborn baby in several diseases and pathological conditions.

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MEDICO SOCIAL PROGNOSIS OF CHILDREN WITH EPILEPSY

EPIDEMIOLOGICAL STUDY AND ANALYSIS OF 245 PATIENTS

BY MATTI SILLANPÄÄ

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM

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TO MY FAMILY

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ACTA PAEDIATRICA [illegible]

SUPPLEMENTUM [illegible]

From the Department of Paediatrics [illegible]
University of Turku [illegible]

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CONTENTS

DEFINITIONS

Epileptic seizure	spontaneous cerebral seizure without demonstrable external or internal cause or continuing infection
Epilepsy	recurrent epileptic seizures
Occasional seizure	epileptiform, grand mal like seizure resulting from known external or internal cause or continuing infection
Status epilepticus	convulsive grand mal status without regaining of consciousness between single successive seizures or seizures lasting one hour or more
Prevalence	number of patients living at a specified point of time per unit of population
Incidence	number of new cases diagnosed at a specified period of time per unit of population
Irritative EEG manifestation	EEG manifestation with spikes or sharp waves or both, as such or combined with slow waves
Non-irritative EEG manifestation	EEG manifestation without spikes or sharp waves

LIST OF ABBREVIATIONS

ADL	activities of daily living
EEG	electroencephalography electroencephalographic
GM	grand mal epilepsy grand mal epileptic
PM	petit mal epilepsy petit mal epileptic
IQ	intelligence quota
PEG	pneumoencephalography pneumoencephalographic
C.S.F	cerebrospinal fluid
SpW	spike and wave, spikes and waves
Hz	Hertz

I INTRODUCTION

The symptom of epilepsy is one of the commonest chronic neurological problems in childhood. No less than 90 per cent of adult cases of epilepsy have started before the age of 20 (8, 214, 217).

Opinions on the prognosis of children with epilepsy are far from unanimous. The differentiation of epilepsy from single epileptiform attacks of occasional situational character may be difficult. Definitions of different types of epilepsy classified on more or less accurate grounds have altered from time to time. Rodin (280) recently drew attention to the terms "improvement" and "recovery" from seizures. These terms have been considered identical by some authors and, therefore, too favourable results obtained. He also pointed out that the follow-up period of one or some few years is not enough to give a correct picture of long-term prognosis for such a chronic disorder as epilepsy.

Since a clear controversy of opinions still exists and only few up-to-date works are available on the prognosis of children with epilepsy, a retrospective study was made to investigate the prevalence and incidence of different types of epilepsy and to elucidate the present medico-social prognosis of child epileptics in South western Finland. The patients of the collected series will be prospectively followed up at regular intervals.

II REVIEW OF THE LITERATURE

A. PREVALENCE AND INCIDENCE OF EPILEPSY

Convulsive disorders are rather prevalent occurring in 4—8 per cent of the average population (31, 41 53 62, 314) As to the prevalence of epilepsy lower figures are usually presented. Additionally there are only few studies which to a sufficiently accurate degree are limited as to geographic area time and the concept of epilepsy

Baldwin *et al.* (15) studied the population below the age of 21 of 3 6 millions in Maryland, USA and found the prevalence rate of 5 0 per 1000

Kurland (198) investigated the total population of 30 000 in Rochester Minnesota, for epilepsy Only patients with seizures during the previous five years were taken into consideration The total prevalence rate was 3 65 per 1000 (males 4.98, females 2 61) The rate for GM was 2.31 for PM 0.2 and for psychomotor epilepsy 0 64 per 1000 The average annual incidence rate was 29.8 per 100 000 population. The incidence rate for different five year groups was as follows 152.0 per 100 000 for 0—4 25.3 for 5—9 24 7 for 10—14 and 18 6 for 15—19 years of age respectively The rate for those aged 0—19 years was 67 8 per 100 000

Fisher *et al* (75) in their study of the frequency of epilepsy in close relatives of epileptics, found that the risk for major motor seizures was 7 6 per cent by the age of 19½ years and 9 4 per cent by the age of 39½ years These figures are valid for the relatives of patients of an age up to 3½ years at the onset of epilepsy which age shows a well known aggregation of familial recurrent seizures (259)

Brewis *et al.* (29) studied the frequency of epilepsy in the city of Carlisle in England. Their investigation revealed that 101 out of 21.384 persons aged 0—19 (4 74 per 1000) had convulsions. The average annual incidence rates for five-year groups in this investigation were as follows 75.3 per 100 000 for 0—4 36 0 for 5—9 44.3 for 10—14 and 53 4 for those aged 15—19 respectively The average incidence per year in patients aged 0—14 was 36.8 and in those 0—19 years of age 37 0 per 100 000

In Scandinavian countries, the reported prevalence rates are grossly the same although lower figures have been presented, as in Krohn's report (191) He studied the prevalence in northern Norway where the total population numbered approx. 416 000 The patient data were collected through personal contact with local private practitioners and through the case records from different local and special hospitals and departments. Altogether 951 epileptics were found (2.3 per 1000) However the frequency maximum was definitely in lower age groups and, if these ages only were considered, the prevalence rate would be markedly higher

Gudmundsson's (116) clinical and epidemiological investigation on epilepsy in Iceland was based on information from inpatient and outpatient departments, private and general practitioners and laymen, and comprised the whole country The prevalence

rate for patients 0—9 years of age was 2.49 per 1000 in the population of 43.807 and 4.35 per 1000 in 32.872 aged 10—19

Bronson's (32) sample consisted of 194 cases from the population of 67 000 below the age of 21 in one Swedish county The patients fulfilled the given criteria for residence and the commonly accepted definition of epilepsy Those patients were included who had had at least one defined epileptic seizure (33) during the previous three years. The prevalence rate was 3.5 per 1000 for persons 0—20 years and 4.0 per 1000 in the group aged 7—20.

In Finland the first extensive epidemiological investigation of epilepsy was published in 1924 (311) In this detailed study by the Central Statistical Office of Finland which comprised the whole country and all age groups, the purpose was to find all patients with genuine epilepsy Altogether 2294 cases or 0 67 per 1000 were found. The figures were obviously too low but gave some idea of the distribution of epilepsy in the country In the county of Turku and Pori, which includes the South western part of Finland, the prevalence rate was 0 79 per 1000 thus exceeding the figure for the whole country

In 1942, Kalla (178) reported the prevalence rate of 1.34 per 1000 in the population aged 15—19 years based on studies by the Central Statistical Office of Finland.

The prevalence and incidence of epilepsy during the first year of life was 10 per 1000 in the study of Mäkinen (251) which comprised 86 per cent or 10..89 of all the new born babies born in 1966 in the two most northern counties of Finland.

Basing their conclusions on the figures for patients receiving anticonvulsant drugs free of charge by virtue of the Sickness Insurance Law Hakkarainen *et al.* (122) obtained the prevalence rate of 2.03 per 1000 for those aged 0—15 years and 2.74 for the total average population of the country A somewhat higher rate was found for the total population in the Turku University Central Hospital (TUCH) region, namely 2.89 per 1000 On the basis of an earlier study the authors observation was, however that not more than two thirds of the patients took advantage of the drugs available free of cost and, therefore, the figures given above should be at least one third higher Thus, the rate for the total population in the TUCH region should be 3.85 per 1000 and for the age group 0—15 years 2.45 per 1000

B. MEDICAL PROGNOSIS

General prognostic aspects

Opinions on the prognosis of children with epilepsy have greatly varied since the time of Hippocrates (460—377 B C) who was the first to take a position on the outcome of epilepsy in children. According to him, mortality of small children with epilepsy is high but youths and young adults may recover if adequately treated (320)

Subsequently the prognosis was regarded as sometimes good, sometimes bad, until the advent of anticonvulsant drugs, which were hoped substantially to improve the results. These expectations have not been fulfilled (280 281) Seizure prognosis seems to have been the same during the twentieth century Favourable impressions created by several authors of the reports during recent decades were based on the liberal interpretation of results in that sense that freedom from and improvement of seizures were identical (280) Furthermore, the long-term follow-up of three to five years was not achieved in most papers. It is evident that the longer the follow up the more frequent the relapses (31 330) as a consequence of the intermittent course of epilepsy with remissions and relapses typical of this chronic disorder

Another point is that prognosis of epilepsy is more than that of seizures. The onset of extremely grave types of epilepsy such as

infantile spasms and akinetic-myoclonic seizures depends on typical age and low maturation degree of brain (163, 266) but these types have, on the other hand, a tendency to disappear with increasing age. In infantile spasms, for instance, the main problem is not seizures but common mental retardation, social immaturity emotional maladjustment and high mortality (35 44 101) Due to these factors, the *total prognosis* of the patient, i. e prognosis for seizures, intelligence schooling capacity for work and behavioural, emotional and social adjustment should always be evaluated to obtain an idea of the patient's need for habilitation and eventual recovery from epilepsy (250) It is even better not to strive for a complete freedom from seizures, which may eventually only be obtained by the use of almost toxic doses, thereby hazarding a patient's alertness and mental activity On the other hand, treatment of a maladjustment in a patient handicapped by social circumstances in the home directly related to an epileptic state should be preferred to the treating of some few fits a year (334)

By far the greatest number of patients with recurrent epileptic seizures have had the onset before the age of 20 (3, 171, 214, 217) General agreement seems to prevail in text books (27 112, 240) that permanent recovery from seizures is rarer in these cases than in those with onset after the age of 20. However Gross (114) and Habermaas (120) could not draw any prognostic conclusions in relation to age at onset. Indeed, no differences could be found between percentages of terminal remissions between adults in Rodin's (280) Table 1 (p 4) and children in Table 5 (p 24) in his monography on the prognosis of patients with epilepsy The figures in the tables were collected by Rodin from the papers published in 1901—1964 If one counts the mean percentages of patients who had recovered, the mean for adults is 28 per cent and that for children 32 per cent. The median percentage for the two groups is 32 per cent. No significant difference then seems to exist.

Suggested factors contributing to prognosis

Sex. There is a general opinion that sex is not related to prognosis (189 308) However Gowers (108) concluded that the outcome would be slightly better in males. Dalby (58) stated that females have a significantly poorer prognosis than males in all types of epilepsy

Age at onset As Rodin (280) has pointed out, it is quite difficult to decide what should be regarded as the age of onset of epilepsy because recurrent seizures may be preceded for *months or years* by single occasional fits. The question whether the first epileptic attack or starting of recurrent seizures has been taken as the age of onset often remains unanswered in reports on epilepsy

Habermaas (120) and later Lempp (202) Lundervold and Jabbour (227) and Rodin (280) did not find any significant correlation between age at onset and prognosis of seizures. On the other hand, there are numerous papers indicating the significance of age at the onset of recurrent seizures.

Neonatal seizures are generally considered to have a bad prognosis with the high mortality of 20 to 42 per cent (34, 38, 54, 238) and the high recurrence rate of seizures (185 290) The prognosis is worst if there is a severe basic disease (290) Neonatal seizures may also have a tendency to spontaneous disappearance even though the recurrence after a seizure free interval of years is possible (16) The conclusion of Joppich and Schulte (173) wast that prognosis of neonatal fits is favourable if the basic disorder is manageable or transitory if the pathology of the electroencephalogram is of a short duration, or if the neurological state is normal since delivery or for a short period thereafter However in some familial cases with frequent generalized convulsions and attacks of cyanosis up to three weeks of age the prognosis may be excellent (21)

The onset at infancy or early childhood is considered to carry a less favourable prognosis

than in late childhood and adolescence (91, 132, 141, 188, 330) The outlook is further worsened by certain types of epilepsy namely infantile spasms and akinetic-myoclonic seizures. Epilepsy starting in puberty was regarded to have a good prognosis by Turner (320) Kiorboe (188) disagreed with this opinion.

Aetiology Due to the fact that basic mechanisms of epilepsy are still unknown, the aetiological classification simply consists of idiopathic or cryptogenic and symptomatic varieties in most reports. The terms genetic hereditary genuine and unknown are intermixed or treated as a nonorganic entity in the literature (3, 40, 91) However an unknown aetiology is not equivalent to a hereditary cause and may be organic as well.

From the prognostic point of view epileptics with an unknown or probably known aetiology have a better outcome than those with a defined cause (8 31 91, 112) with the exception of psychomotor epilepsy (174) There is also a difference between non familial and familial cryptogenic cases the former have a better prognosis than the latter (268) An even more significant observation is that occasional convulsions or recurrent fits in close relatives does not imply a bad prognosis (320) but a favourable one (31 55 177) contrary to earlier opinions (108, 120)

In symptomatic epilepsy the seizure prognosis may be variable (40) but is generally considered worse than in cryptogenic cases (16 308) The more or less well-defined organic aetiology is most usually found in infancy and early childhood (16, 270, 280, 294) and is probably for the most part responsible for a less favourable seizure prognosis at that age.

Some authors have not found any relationship between organic brain disease and prognosis (188, 280 320)

Psychomotor state. There is a general consensus of opinion that epilepsy in patients with mental or motor retardation or abnormal neurological signs is often refractory to treatment. (132) In patients with epilepsy and cerebral palsy the neurological abnormalities are present significantly earlier than in those without epilepsy (106) the former also having a poor long term prognosis for seizures (10, 148 280 308) The normal neurological state, on the contrary would favour a good outlook (225)

Sleep-waking cycle Since very early times it has been observed that sleep and epileptic seizures are closely interrelated (193) Charcot (45) drew attention to the tendency towards regularity of recurrent seizures. Janz (157 160) has published detailed studies on awakening sleep and diffuse epilepsies.

From a prognostical point of view some observations are worthy of notice No correlation between prognosis and the sleep-waking cycle was found by Hedenstrom and Schorsch (13?) and Strobos (308) A good prognosis in cases with seizures in either waking or sleeping epilepsy only was noted by Gowers (108) in waking and awakening epilepsy by Turner (320) and in sleep epilepsy by Kiorboe (188) and Livingston (217) Probst (274) felt that a poor outcome was more frequently met with in nocturnal than in daytime seizures. Janz (160) found the best outcome in cases with awakening epilepsy and the worst in cases with both awakening and sleep epilepsy

In epilepsies with nocturnal seizures, waking EEG is not infrequently normal (1, 49) while in awakening epilepsy there is often both slow background activity and spikes and waves of variable frequency and amplitude in EEG (49)

The role of the sleep-waking cycle in prognosis for GM and psychomotor epilepsies will be treated later on.

Clusters of seizures i.e. occurrence of several seizures on one or more successive days with subsequent seizure-free intervals of several

weeks, is a prognostically ominous feature. It was uncommon in a group with freedom from seizures in the series of Rodin (280)

Seizure frequency Seizure frequency may have some influence on prognosis. The fewer the seizures, the easier they will be treated (206 222) No such correlation was, however found by Ranheim *et al* (275) It is to be considered, too, that a marked difference exists between single seizure types, *e g* GM or PM or mixed fits.

Duration of seizure illness Kiorboe (188) found that more patients with a short (less than one year) duration of illness belonged to a group with final or temporary remissions than to another group with no remission. Holowach *et al* (1946) came to the same conclusion relapses were frequent in cases with more than six years illness before control. Bridge (31) did not discover any difference in this respect.

Status epilepticus. The incidence of GM status epilepticus in epileptic children has been thought to be no less than 8 per cent (206) The occurrence of one or more GM statuses is a bad prognostic sign (6, 114 206 280) In one of the more noteworthy recent studies (6) where the age of occurrence of statuses was during the first year of life in 37 per cent and during the first four years of life in 85 per cent of the total 239 cases, the early occurrence was thought to be related to organic aetiology and often to gross brain damage. On the other hand, in 47 cases no neurological abnormalities were observed before the status, a considerable neurological deterioration, however being demonstrated after it. The prognosis of the total series depended on age 78 per cent of infants under 6 months, 58 per cent of those from 6 months to 3 years and 45 per cent of those over 3 years had developed grave neurological abnormalities after the status The prognosis was also related to sex boys were more often affected in the symptomatic group while girls predominated in the cryptogenic group Jacobi (156) too, stated the high frequency of brain damage after one or in particular recurrent statuses. Brain ventricle dilatation could be demonstrated with PEG following status epilepticus (5) The longer the single status and the higher the frequency of statuses is, the worse is the prognosis 163 165) The prognosis is also serious in newborn status epilepticus (71)

Drug therapy Duration of illness prior to treatment is generally considered prognostically significant in that the shorter the pretreatment period the better the prognosis. However in cases with only few seizures and a marked tendency to spontaneous recovery excess weight may have been attributed to the beneficial effect of drugs. Infrequent seizures prior to treatment (108, 112, 320) and during it (108, 206) carry a favourable prognosis. A considerable refractoriness to treatment is common in cases with predominantly tonic (95) myoclonic (280) or hemiconvulsive (94, 239 308) seizures.

Selection of drugs is obviously important for seizure prognosis. Without going into particulars, some points are worthy of mention. Based on both clinical and EEG observations a conception has grown up that in sleep epilepsy too deep a sleep and in waking epilepsy sleep disturbances, at least in part, provoke seizures. As a consequence, phenytoin is suitable for sleep epilepsy but ineffective against waking epilepsy and even against pure PM attacks (159) As will be seen later the two latter types are closely related (49 159 160)

Interruption of therapy is often a difficult matter to judge. It is well known that an abrupt discontinuation of medication may provoke seizures or status epilepticus. This holds true particularly for patients receiving phenemal or phenytoin and for those with GM seizures (217) In paediatric patient series, gradual withdrawal of drugs may cause a

recurrence of seizures in 25 to 40 per cent of cases (148 175, 176 337) but even as many as four out of five patients has been claimed to suffer a relapse (59) Zenker *et al* (337) gave some criteria for judging the withdrawal of therapy but the difficulties in this regard are considerable (176) Abrupt discontinuation of medication is contraindicated (257)

One of the most recent papers on this topic is the report of Holowach *et al* (148) In their series of 148 paediatric cases (of which 82 had simple febrile convulsions) followed up 5 to 12 years after withdrawal of drug treatment they found a recurrence rate of 24 per cent of the cases. The lowest recurrence rate was in GM (8 per cent) and PM (12 per cent) the highest in "jacksonian" (53 per cent) and combined seizure types (40 per cent) Psychomotor attacks relapsed in 25 per cent of cases. Like Strobos (308) they did not find any clearly significant correlation of prognosis to sex or positive family history neither to puberty which has been commonly considered to be a high risk period for recurrence of seizures in the case of discontinuance of drug treatment (176, 214 217 337)

The minimum of four years seizure free period and one to two additional years for gradual withdrawal of medication is regarded as a good practice by Livingston (217) The recurrence rate is highest during the first two years after discontinuation (175 217) and especially high shortly after the discontinuation (176) This rate is not influenced by the length of gradual withdrawal if it is between one and three months (175) Cases with early onset of seizures, with known or suspected organic aetiology and mental retardation carry a poor prognosis (148, 308) Unlike Juul-Jensen (175) Livingston (217) maintains that recurrent seizures after withdrawal of therapy are rather drug resistant

Normal or normalizing EEG in the withdrawal suggests a favourable outcome (101 308) and may prognostically be even more important than the normality of initial EEG (188 227) However the contrary is not true EEG may be abnormal for years after the cessation of seizures (199)

Prognostical significance of EEG One of the first authors to use EEG in judging the treatment results were Hoefer *et al* (145) They found that normal EEG was more common in adequately treated cases though in most patients, full normalization was not achieved. Lempp (20) and Livingston (214, 217) could not find any relationship between normal or abnormal EEG on the one hand and prognosis on the other apart from the classic bilaterally synchronous SpW discharge of pure PM. He also drew attention to the fact that "in many children the EEG tends to revert to normal during adolescence regardless of their clinical progress." (215) However numerous reports on a more or less clear relationship between EEG and seizure prognosis have been published (2, 41 196 227 241 281)

Neonatal EEG has been prognostically evaluated in several reports (77 126 245 246, 247 316) in the first month or first few years of life, but only a smaller number of cases had convulsions. In the series of Monod and Ducas (246) 97 out of the total 161 had neonatal fits. Fifty seven per cent of cases with convulsions and 95 per cent of those with status epilepticus had very abnormal EEGs. Based on 45 cases with clinical or electrical seizures in the series totalling 270 newborn babies Monod *et al* (247) found a poor outcome in cases with typical or atypical clinical seizures and without any paroxysmal electrical discharge in either interictal or perictal record. A poor outcome was also found in cases with electro-clinical seizures and with paroxysmal electrical discharges without any clinical seizures. The authors emphasized that EEGs of the greatest prognostical value are obtained during the first week of life, since features of pathological significance will disappear after the

first postnatal week and EEG will become less informational.

After the neonatal period, the abnormal clinical course, judged on the basis of deviant EEG is the commoner the younger the patient is (241) Normal initial EEG carries a good outlook (2, 41 184, 206 226 227 281) but not beyond the age of 15 (323)

Normal background activity without spikes or other foci implies a successful outcome (196 281) while slow background activity or slow SpW diffuse patterns would suggest a poor prognosis for both seizures and mentality (41 247 281)

Occurrence, site and constancy of one or more EEG foci also influence the outcome. Local findings in a normal background activity carry a favourable prognosis (247) The site of the focus or foci in one EEG was given no prognostical weight by Hess (141) nor by Isler and Hess (154) Patients with occipital (98) centroparietal (808) or in particular mid temporal (103) SpW foci have a good chance of later recovery from seizures, while cases with unilateral or bilateral anterior temporal foci are prognostically less favourable as a consequence of common organic aetiology and well-known drug resistance.

Prognosis is also unfavourable when foci are bilateral (126) multiple (91, 156) or when there are bilateral paroxysmal discharges or abnormalities involving the entire hemisphere (808)

The inconstancy of the site of EEG foci is of prognostical significance. EEG spike foci in childhood may migrate from the occipital to the temporal region (99 103 318) or in a contralateral direction (101 228) Successive foci also occur with changing localization and without any systematic order apparently only as various expressions of subcortical epilepsy (266) possibly originating from deeply situated primary focus (235) Foci with changing localizations are often of a functional type and prognostically favourable (101)

As to EEG patterns characteristic of some types of epilepsy the ominous outlook of hypsarrhythmia and "spike and wave variant" and the more favourable regular bilaterally synchronous three Hz SpW rhythm will be taken up later in connection with their corresponding clinical types (p 17) Paroxysmal slow activity and 14 and 6 Hz positive spikes occurring more infrequently in childhood have a relatively good outlook (41, 98, 187) Whether this rhythm is an abnormal phenomenon at all is questionable, inasmuch as it occurs not infrequently in normal children without any clinical signs of disease (74 104 242)

The EEG is of limited value when judging the results of drug treatment (269) Lennox (206) pointed out that prognosis does not depend on the intensity of pretreatment potentials but on the responsibility to anticonvulsants. Dramatic dissolution of gross abnormality is possible without medical therapy On the other hand, freedom from seizures is not inevitably followed by normal or normalizing EEG (217 308) The first three months are important in this regard (224, 281) Anticonvulsant drugs may also have prognostically misleading changes in EEG such as slowing of background activity during phenytoin therapy (281)

Pneumoencephalography Jacobi (156) found a poor outlook for cases with dilated ventricles, or hemispheric or cortical atrophy Similarly Juul-Jensen (174) had previously stated that more considerable changes of atrophic character were in proportion to a poorer prognosis. Hedenström and Schorsch (132, Kiørboe (168) and Lundervold (225) could not find any significant correlation between the prognosis and either the first or follow-up PEGs.

Prognosis in different types of epilepsy

Although the advent of EEG (20 100) made the classification of epilepsy in some respects easier opinions are still far from being unanimous. In *Table* 1 there are some classi-

Table 1. Classifications of epilepsy given in the literature

Author(s)	Grand mal or generalized	Petit mal or absences	Infantile spasms or BNS attacks	Akinetic myoclonic or Lennox syndrome	Minor motor seizures	Myoclonic	Focal	Partial cortical or Jacksonian	Psychomotor or temporal lobe epilepsy	[illegible] or [illegible] epilepsy
Hess and Neubaus 1952 (142)	+	+	+	+		+			+	
Livingston 1954 (214)	+	+			+				+	
Bamberger and Matthes 1959 (16)	+	+	+	+				+	+	
Nuffield 1961 (250)	+	+	+	+			+		+	
Janz 1969 (163)	+	+	+	+				+	+	
Livingston 1972 (217)	+	+			+	+			+	+

Table 2. Classification of epilepsy used in the present study compared to the International Classification f Epileptic Seizures (93)

Present study	International Classification
Partial cortical seizures	Partial seizures with elementary symptomatology
Psychomotor seizures	Partial seizures with complex symptomatology
Partial seizures secondarily generalized	Partial seizures secondarily generalized
Pure petit mal seizures	Absences
Grand mal seizures	Generalized, bilateral symmetrical clonic, tonic or tonic-clonic seizures Unilateral or predominantly unilateral seizures
I fantile spasms	Infantile spasms
Akinetic-myoclonic seizures	Atonic seizures, akinetic seizures
Unclassified epileptic seizures	Unclassified pileptic seizures

fications from the last two decades. As can be seen, GM, typical PM and psychomotor epilepsies are generally accepted while infantile spasms and akinetic-myoclonic seizures are by some authors put under the same heading of minor motor seizures. A difference has also commonly been made between partial cortical or jacksonian and, on the other hand, other partial seizures. Recently a final proposal for an international classification has been made (93). Different seizure types are defined in the present study in accordance with this proposal, with a preference of clinical signs and symptoms in uncertain cases.

In the following review of the literature and later when treating the present author's sample, the classification chosen is presented and compared to the international classification in *Table* 2.

Partial cortical epilepsy The age at onset was stated by Hess (141) to influence the prognosis of partial cortical seizures. Remissions were significantly more frequent in cases with the onset at 0—4 years than later and in [illegible] centrencephalic type. The greater the age of onset the smaller the difference. Virtually no remissions were found in cases with the onset after age 9

Partial cortical epilepsy is often combined with GM seizures, which are in 50 per cent [illegible] or diffuse (or independent of the [illegible] of day) in 3[illegible] per cent of sleep epilepsy and in only 1[illegible] per cent of the waking epilepsy ([illegible] 163) Partial cortical seizures are then [illegible] associated with GM occurring regardless of the sleep-waking cycle.

Psychomotor epilepsy Opinions on the seizure prognosis of psychomotor epilepsy are comparatively uniform a quarter to one half of patients will become *free from seizures* (43 146) while the rest are more or less refractory to treatment or quite intractable (91 141 219 227) Currie *et al* (56) maintained that prognosis is relatively good, independent of age. The impression of Chao *et al* (43) was that the outcome is "much more favourable in children than in adults. The less favourable outlook for psychomotor epilepsy partly depends on the fact that it often occurs combined with other seizure types, which combinations make the prognosis substantially worse (80)

Sex may be of significance in psychomotor seizure outlook. Matthes (234) stated that in females, milder forms of uncombined seizures predominate.

The age at onset, whether in childhood, adolescence or adulthood, had no influence on seizure outcome in the series of Currie *et al* (56)

The role of aetiology is of considerable importance. Janz, in his extensive report on the special pathology and therapy of epilepsy (163) classifies the psychomotor epilepsy into pure seizures without, and combined ones with, *other types of seizures* and, *on the other* hand, into primary where psychomotor epilepsy is the first occurring type in a patient, and secondary forms with psychomotor fits following other types of epilepsy

In primary psychomotor epilepsy which was not infrequently found by Falconer (78) *spontaneous recovery from seizures* occurred in seven per cent of cases during the follow up period of 20 years in the series of Janz (163) More than half the patients remained uncomplicated by other types, even without any medical treatment, but the seizures were relatively refractory to therapy which was *started later* There was an essential difference in seizure prognosis according to whether psychomotor epilepsy was complicated by GM in the course of the first three years after onset or later The earlier the combination with GM, the greater was the risk that combined GM is of the sleep epilepsy type with a *frequently progressive* course The opposite, a late combination was commonly of the waking epilepsy type with a benign oligepileptic course. There was also an increasing risk for a less favourable "diffuse epilepsy if combined GM was *of* long duration (162, 163 200)

According to Janz (163) psychomotor epilepsy is combined with sleep GM in 55 per cent with "diffuse" GM in 30 per cent and with the most benign form waking GM, in 15 per cent of cases. He also claimed that *isolated sleep GM seizures and* psychomotor seizures are, as evaluated in EEG mostly expressive of temporal lobe epilepsy while isolated waking GM attacks and age-dependent minor motor seizures are expressive of centrencephalic epilepsy and involved with a strong endogenous disposition. Symptomatic psychomotor epilepsy has then a poorer prognosis than a centrencephalic or idiopathic type.

Secondary psychomotor epilepsy is considered to develop as a result of GM seizures, particularly after febrile convulsions (?06, 235 260) and after single or repeated epi-

bl 3. Recovery from seizures in pure petit mal according to the literature

uthor(s)	Number of patients examined	Minimum duration of follow-up (in years)	Percentages of combined other seizure types	Percentages of patients remitted from PM	Percentages of patients remitted from all seizures
ridge 1940 (31)			25		10
anz 1955 (158)	163	10	53		16
urner et al. 1963 (57)	82	15	37	44	34
aal 1957 (262)	38	6	32		36
Kuhlo 1965 (197)	76	6	35		40
Hertoft 1963 (140)	50	8	38	56	48
Dalby 1969 (58)	160	5	46	79	58
Doose and Schaffner 1962 (68)	09	2	27	86	59
Holowach et al. 1962 (147)	72	1	61		63

leptic statuses (260) From a prognostic point of view the organic damage suggested to develop in connection with the abovementioned or other equal states (73, 92, 231, 260 286) obviously signifies a poor prognosis, because psychomotor epilepsy with local temporal findings in EEG is found twice or three times as frequently in institutionalized as in ambulatory patients (18)

As to the seizure pattern of psychomotor epilepsy frequent fits, particularly with post-ictal amnesia, suggest a less favourable prognosis (206)

A good response to anticonvulsant therapy is often gained in cases with chiefly autonomic symptoms (42, 69)

EEG may give some clue to the prognosis. Midtemporal focus is known to be related to a good outcome (23, 103) Anterior temporal focus is associated mostly with organic damage in the temporal lobe as stated above, and is refractory to therapy

Petit mal epilepsy PM was for a long time considered as a benign disorder outside the epilepsy category (89) and prognostically good (4) *As early as 1907 however Turner* (320) pointed out that prognosis for PM is poor but he gained no support. Since the discovery of the typical electroencephalographic pattern (100) the clinical and especially differential diagnostic and associated prognostic features of PM have been better understood.

Earlier conceptions on the favourable prognosis in PM have not gained success in more recent reports. As seen in *Table* 3 from 10 to 63 per cent of patients had become free from seizures during the follow-up time of 1 to 10 years. Seizure freedom clearly depends on the length of the follow up period. Holowach *et al* (147) stated that there is no difference in the seizure prognosis between PM and other seizure types. According to Janz (158) a spontaneous recovery earlier regarded as *common, is the exception rather than the rule.*

In regard to different factors that may influence the seizure prognosis for PM a combination with other seizure types carries a *less favourable prognosis (58, 140)* like any other seizure combinations as stated above. Even PM status epilepticus is more frequent in patients with PM combined with other *seizure types (197)* which has to be considered a bad prognostic sign (220)

Age at the onset of PM may sometimes be difficult to determine because fits may remain unnoticed or unassociated with epilepsy by parents (197) Medical therapy is typically started often months or years after the onset (68) or not before other seizure types are combined (163) Kuhlo (197) was not able to relate the age at onset to seizure prognosis. Hertoft (140) found no difference in prognosis between groups with the first attacks either before or after the age of 7 Instead, Currier *et al.* (57) claimed that " favourable signs may include early onset (between 3 and 10 years) Hess (141) stated that seizure prognosis is poorer for PM if it has started after the age of 9 Lees and Liversedge (201) concluded that PM tends to begin before the age of 15 and that the later the onset, the more frequently GM is associated Dalby (58) Lennox (206) and Livingston *et al* (220) confirmed the conclusion of poorer prognosis in cases with a late onset. Even very few GM attacks are of significance (17 58) but a single attack is not (140) The same holds true for cases with preceding GM (50 68)

There is no agreement as to the role of sex in PM prognosis. Dalby (58) stated that females more frequently have a late onset and associated GM while Paal (262) Pache (263) and Kuhlo (197) found the same for males Gibberd (97) and Hertoft (140) were not able to show any difference between sexes in this regard.

In cases with automatisms the seizure prognosis could not be found less favourable (57 68) as was claimed by Christian (50)

The role of puberty seems to be significant PM seizures tend to become fewer shorter and gradually disappear (197) while GM often manifests itself (58, 220)

The short duration of illness (under three years) carries a good prognosis, independent of seizure frequency (57) There may at times be difficulties in judging the stopping of seizures because patients often learn to live with them and do not take any notice of single fits (201) False information on discontinued seizures is then inadvertently given by the patient

As to aetiological aspects, a positive family history of epilepsy does not imply a bad prognosis 57 68) Brain damage in PM carries a bad prognosis according to Livingston *et al* (220) but Dalby (58) stated that it does not influence the prognosis, although it will increase frequency of seizures and a tendency to an earlier onset of GM.

Grand mal epilepsy has a good prognosis when occurring alone (10) and essentially better than that of psychomotor seizures (174, 188)

Age at onset is related to outcome. The later the onset of GM the better is the prognosis. There is, however a tendency to a recurrence of stopped seizures in puberty (217)

As to the correlation between the prognosis and the time of day when seizures usually occur a good outlook is to be expected in cases with awakening epilepsy (163) which may occur as single GM fits and is in 90 per cent of cases of idiopathic origin (160) In waking epilepsy attacks are usually irregular (163) If periodicity begins to occur it signifies a tendency to sleep or "diffuse types (163) or as in girls in puberty a connection with menstruation (16) and refractoriness to therapy (217) Awakening epilepsy however displays in only 6 per cent of cases a tendency to less favourable types compared with 20 per cent of cases with sleep epilepsy (163) Waking epilepsy is also mostly combined with age-dependent PM types (163)

GM epilepsy is generally considered the easiest to treat with drugs (91 141 217)

Infantile spasms The variable nomenclature for infantile spasms which, for example Bamberger and Matthes (16) and Jeavons and Bower (168) have drawn attention to, is very demonstrative of the difficulties, which this type of epilepsy has evoked as to aetiology seizure pattern, differential

diagnosis and therapy West (329) was the first to describe its symptoms and signs in his own son. Féré (80) was the first to take notice of its variable prognosis. Later a great number of unanimous reports on its bad outcome were published. Now prognoses for the arrest of infantile spasms, normal EEG and normal mental development are with akinetic-myoclonic seizures, its later form of manifestation (102) regarded as the severest form. *Table* 4 (p 27) shows af few samples from the literature

The male sex is more frequently affected in most reports (102, 166 168, 237)

The onset of seizures at the age of 3 to 9 months, common in infantile spasms, carries a better outcome than an onset beyond this age (297)

Jeavons and Bower (168) in their monography on infantile spasms, made an aetiologic division into cryptogenic, symptomatic (perinatal, immunisation, other) and doubtful cases. Three factors emerged, the occurrence of which was shown to have a poor total prognosis, regardless of the aetiology or treat ment with corticotropin or steroids. These factors are 1 initial severe mental subnormal ity 2 other types of epilepsy and 3 hypsarrhythmia. In a further follow up and using the same division, the importance of aetiology over corticotropin or steroid treatment in evaluating the overall prognosis was stressed by Jeavons *et al.* (169) who also demon strated the more favourable outcome in cryptogenic and immunisation groups than in cases with perinatal damage or other symptomatic aetiology concerning school per formance, mental subnormality and neurological abnormalities. Matthes (232) came to the same conclusion as to the good outcome for cryptogenic cases.

The significance of neurological status is stressed by several authors. A good outlook may be expected for patients with normal development up to the onset of spasms and with no neurological abnormalities (297) Initial severe mental subnormality is, instead, considered as a bad sign (168 288) Motor development has been found grossly normal in many cases (66)

Seizure pattern has caused many prognostic speculations. The outlook is considered bad in cases with salaam type of spasms, combination of lightening nicking and salaam spasms or spasms together with other types of epilepsy with the exclusion of pure PM (101, 168, 218, 288) high daily frequency of seizures (288) which last point, however causes only apparent worsening because the arrest of sei zures may restore the former skills (232) although not completely (44) Several authors (44 101 168, 218) have drawn attention to the spontaneous disappearance of infantile spasms with increasing age However other types of seizures often subsequently occur

The prognostic role of EEG has been eval uated in many reports. Although an occurrence of hypsarrhythmia, the characteristic EEG finding of infantile spasms, is considered by some authors (297 306) to carry a favour able prognosis with corticotropin and steroid treatment it however only deals with freedom from seizures (288) which may be of a short-term character and in no correlation with long-term total prognosis (28) On the contrary cases with hypsarrhythmia in EEG have a definitely bad prognosis according to Jeavons and Bower (168) whether patients have infantile spasms or not (90) If the EEG on the other hand, is normal within the first year of life in connection with infantile spasms, the outlook is significantly better especially for mentality (35) A good correlation between normal EEG and good seizure outcome was also reported by Schmidt (288) and Gibbs *et al.* (101)

A prognosis for cases with defined abnor mal EEG before the onset of infantile spasms was elucidated by Schmidt (288) who was able clinically and electroencephalographically to follow up nine patients with pathological EEG six of whom had local and three diffuse changes. These patients belonged to the symptomatic group with an abnormal previous

history and pathological neurological and PEG findings. They all had a poor total outcome

The degrees of abnormality of PEG findings and mental retardation are in proportion, while, on the other hand, normal PEG is most commonly found in cases with good seizure and EEG prognosis (288, 327) No such relationship was discovered by Zellweger (336)

Treatment must be started as soon as possible after the onset of spasms to obtain favourable response (9 26 28, 59 288 319) or within a month (297) or up to the age of nine months (288, 306) No evident difference between corticotropin and steroids has been found (72, 163) nor have different side effects of steroid therapy any relationship to prognosis (288) According to some authors (287 288) hypsarrhythmia is almost the only symptom which can be influenced by these hormones. A good initial response is not related to a good long term prognosis (28, 125) The poor total prognosis for infantile spasms is not effectively influenced by medical therapy (44, 101, 151, 218, 237) The remarkably good results of, among others, Sorel and Dusaucy Bayloye (290) and Stamps *et al.* (301) with corticotropin treatment could not be verified in later reports. The recovery possibly gained may be spontaneous (66)

Notwithstanding, one must agree with Jeavons *et al* (169) when concluding How ever since steroid therapy undoubtedly has a beneficial, though often temporary effect on the spasms and the EEG and because the prognosis is generally so bad it seems worth continuing to use ACTH therapy in those cases where there may be some hope of successful outcome.

Later benzodiazepines have been demonstrated to have a successful effect (113, 121 326 332)

Akinetic myoclonic epilepsy The clinical picture of akinetic-myoclonic epilepsy or Lennox syndrome was described for the first time almost a century ago (155) and EEG findings towards the end of the 1930s (105) Its clinical picture was further delineated by Lennox (204 206) Lennox and Davis (208) and Gastaut *et al* (96) It is most commonly intermixed with infantile spasms, which is no wonder because the two types of epilepsy have partly coincident ages of onset and 6 to 25 per cent of akinetic myoclonic seizures start as infantile spasms (67 96 254, 289) Livingston (214) put the two types under the same heading "minor motor seizures

The general prognosis of akinetic-myoclonic epilepsy is one of the poorest of all epilepsies (96 102, 254) often resulting in institutionalization (217) However long-term follow-up studies are as yet lacking (96 163 289) Only few separate mentions of its rarity after puberty exist (266)

The seizure prognosis is more favourable in spite of frequently combined GM seizures (194 289) in cases with an onset at the typical age of 2 to 4½ years. In cases with an onset beyond this age, the frequency of symptomatic aetiologies, akinetic-myoclonic statuses and lacking clinical uniformity of seizures is higher and the total prognosis often poor Both symptomatic aetiology (214 221) and a combination with other seizure types (31, 194) are common.

The role of EEG follow up studies is of little prognostic significance because considerable inter individual and intra individual variability of EEG prevails in the course of the illness (180)

Although the effect of medical therapy is sometimes difficult to evaluate because of capricious periods of spontaneous freedom from seizures (254) the refractoriness to treatment is generally known. In particular this is so in cases with an early onset (194) Of newer drugs, only benzodiazepines have given any advantageous affects (113 121 289 326)

C SOCIAL PROGNOSIS

Intelligence

There are numerous papers on intelligence in epileptics which with few exceptions, refer to more or less significant *mental retardation* deduced from IQ determinations. However the IQ of an epileptic may show anything between idiocy and exceptional talent (87 307) as can also be concluded from many great men with epilepsy in history (?06) The mental level of epileptics varies con siderably from report to report due to the fact that patient series are often selected and based on cases in institutions, psychiatric outpatient clinics or hospitals or limited to certain concise age groups. The results of studies of extramural patients are quite different (?65) Uniform conception is, therefore, often difficult to obtain (162)

There is a variety of test methods, too, which also has its effect on results. The validity of results not infrequently suffers from the inadequacy of research techniques (172) especially in tests for brain damage (335) Furthermore, the concept of normality is variable as to borderline cases with an IQ of 70 to 89 or dull normals. Some consider them as normals, most as mild subnormals.

Attention has been aptly paid to the fact that IQ is not a sole criterion of intelligence (30 144) and not even a valid one in several cases where emotional disorders, slowness of mental reaction, lack of concentration and short memory span essentially worsen the performance capacity in a test situation and an incorrect idea of a patient's intelligence is obtained by an examiner (83 202, 315) Per formance capacity is made still worse by the overprotective attitude of parents and teachers who do not demand so much of them as of other children of the same age (110)

Changes in intelligence level Serial studies on intelligence, behaviour and psycho-social adaptation are essential when judging the total prognosis of an epileptic (1_) In such re-studies, changes in mentality in either a positive or negative direction may be con siderable, ranging from scores of —44 to +24 (83 143, 205) Patterson and Fonner (267) concluded that there is a considerable indivi dual variation of either a rise or decline of IQ at any mental level and independent of the frequency and severity of seizures or medication. The variability of the level of intelligence was also stressed by Dawson and Conn (61) However no defined difference between epileptic intelligence impairment and that of other mental impairment states has been demonstrated (81)

Factors influencing intelligence Chaudhry and Pond (47) compared their patient series to a matched control group with no mental deterioration. No difference was found between the two groups as to age at the onset of brain damage or of seizures. Early age at the onset is, however considered to signify a higher risk for mental deterioration by many authors (51, 52, 87 1?4, 184, ?03, 206) on the basis of cerebral immaturity (16) As has been mentioned above (See p 11) cases with an early onset of seizures not infrequently have an organic aetiology which is commonly associated with mental defects (11, 51 186, 206 280) of different degrees (87)

The observation of Halstead (124) was that abnormal EEG which is not necessarily suggestive of epilepsy or does not show gross abnormalities, is common in cases with a mental defect.

High frequency (31, 47 186, 222) severity (12, 31, 222) multiplicity (31) and serial occurrence (320) of seizures and a long du ration of seizure illness (12, 31) carry a less successful outlook. However the influence of these factors is not so strong as that of he redity and brain damage according to the twin studies of Lennox and Jolly (209)

Schooling

School difficulties are rather common in epileptics (110) Lempp (?03) in his con

trolled study of 55 cases, found in 60 per cent *normal school achievement* while 17.2 per cent of the cases had either an IQ below 80 or other learning difficulties, and the rest had milder problems. Although school achievement is highly dependent on intelligence level and especially correlated with verbal IQ (280) even epileptics with normal intelligence have more school difficulties than others (87). Lately more attention has been paid to psychic factors and mutual social interaction of the patient and his environment (203). Green and Hartlage (110) compared 50 children with epilepsy to a control group without epilepsy by use of performance, social maturity and language tests. They stressed the significance of the parental attitude when they stated that epileptic children scored significantly below the expectancy level in school achievement and language usage. The authors concluded that epileptics have higher potential levels than their performance shows because they are not expected by parents to do the same as normals. They tend to "develop skills which enable them to satisfy personal needs but avoid the development of a behavioural repertoire which requires conforming to demands imposed by peers or superiors." In their later work, Hartlage and Green (127) again emphasized the role of parental attitudes. They found a significant correlation between low academic achievement and two of the parental attitudes, namely disapproval of activity and retardation of development.

Among *factors of possible significance* to future school performance are age at the development of the suggested cause and age at the onset of seizures. As far as pre- or perinatal cause is concerned school *achievement is less* successful than in cases of damage in infancy or later age (203). An early onset of seizures, especially during the first year of life, is associated with poor school achievement and learning difficulties (87, 203, 280). In cases with cryptogenic aetiology of seizures no major learning problems tend to occur (280). Poor achievement is to be expected in cases with GM or mixed seizures (203). The same tends to be the result if temporal focus (203) or poor photic driving (280) is found in EEG.

Employment

The incidence of unemployment of epileptics varies between 10 and 33 per cent, depending on the criteria used (174, 22., 272). In 376 employed patients with epilepsy studied by Janz (164) 35 per cent were clerical, sales and service personnel, 29 per cent unskilled labourers and 18 per cent craftsmen. The remaining 18 per cent were university trained, domestic personnel *etc.* During the course of 4—12 years 2 *per cent* had improved and 8 per cent dropped in social status.

The epileptic worker in the competitive market was studied by Sorel (298) on the basis of 60 patients followed for ten years in the seizure clinic and 16 consecutive epileptic employees followed for 14 years, all in *the constructive sector. Eighty per cent* of these mostly young or middle-aged and skilled labourers with epilepsy showed a good to excellent work record. Their work batch was better and sickness absenteeism less than average while under regular treatment. In Lione's series (213) of 58 epileptics working at two oil refineries the patients had a good attitude towards work and accident frequency and sick days were average or fewer than average. According to Lennox and Markham (210) seizures are not responsible for accidents of epileptics in industry in more cases than in the average employed population. *In epileptics, more accidents occur* due to non-epileptic than to epileptic reasons (161).

Contributing factors to employability. Adequate professional training, optimum control of seizures and continuous specialized supervision by doctors and social workers in collaboration with the patient's family and

working environment all contribute to a successful result (298) Good motivation for work, high verbal IQ self confidence and the patient's present socialization were found by Rodin *et al.* (284) to be favourable features in employed epileptics. A good social milieu, too, contributes to successful employability (222) Dennerll *et al.* (64) compared 87 unemployed to 90 employed epileptics and were able to demonstrate a higher level of intelligence, less difficulties in psychological tests, less neurological and EEG abnormalities and better work history in employed patients.

Intelligence defect and personality changes are the two most important factors which cause work disability (8, 63, 64, 107 272, 280) Weak motivation towards work further increases unemployability (64, 284)

Rodin *et al.* (283) were able to demonstrate a direct relationship between higher employability and higher background frequencies.

It is worth noting that aetiology type or frequency of seizure disorder sleep-waking cycle, or the presence of aura had little or no significance in employability (107 280 284) Instead, poor response to medication matched poor achievement in work (280)

Behaviour

Inter-ictal behavioural disturbances are not infrequent in epileptic children. In different reports their occurrence is 9—65 per cent depending on the criteria used (16 31 87 136 280) Even one or two seizures may be significant in this regard (116) However no behavioural disturbances or personality disorders exclusively characteristic of epilepsy exist (16 31, 310) contrary to an earlier belief based mostly on samples from institutions (124, 177) The commonest symptoms which may occur are irritability slowness with occasional hyperkinesis and temper tantrums, aggressiveness, egocentricity and apathy with periodical rage reactions (177 183)

Contributing prognostic factors. The risk for personality changes is higher in cases with symptomatic epilepsy (87 116, 280) especially when the suggested cause of epilepsy has developed pre or perinatally or during the first year of life (87) or when seizures started early (87 116) Personality development is proportional to intelligence level (87) Rodin (280) stated that epileptic children with normal intelligence and no evidence of organic pathology in psychological tests tend to do well in school and are not likely to present chronic behaviour problems later on" He also found that in cases without behavioural disturbances in the initial examination no such disorders are likely to appear in the follow-up Instead, patients with feeding problems in infancy late talking age, febrile convulsions, organic" features in psychological tests or a psychiatric illness at the onset of seizures have more behavioural abnormalities. Bergemann (19) found the most character disorders in patients with a poor seizure prognosis. Bagley (13) in his taxonomic study suggested that social, psychological and neurological factors are associated with disturbed behaviour and that the variables themselves are largely independent of one another

EEG findings had no obvious relationship to behaviour disorders in several reports (76 212, 312) apart from hypsarrhythmia and "PM variant (280) However Halstead (124) found a tendency towards an association between pathological EEG and bad behaviour Hawkes and Roark (131) noted an abnormal EEG in 90 per cent of epileptics with behavioural problems and Stevens (304) was able to precipitate previously unobtained epileptiform abnormalities in EEG The generally slow activity often observed is related to a disorder in maturation (177)

There is no good agreement as to whether an anticonvulsant *medication* in continuous use produces long-term side effects or not. While some did not find any deterioration of intelligence or behaviour disturbance (31

111 223 296 322) others found increased hyperkinesis (258) exacerbated psychiatric symptomatology while controlling seizures, mental deterioration and folate deficiency (253) or even a state resembling organic psychosyndrome (334) On the other hand the common sedative effect of anticonvulsants may be good for erethic and restless patients (87)

The influence of anticonvulsant on behaviour can now be evaluated considerably better when methods for the determination of blood concentration of anticonvulsants are available Considerable number of the side effects reported may have been caused by toxic doses of drugs, and restudies are necessary to evaluate the long term side effects of anticonvulsant drugs correlated to their blood concentrations.

Psycho-social adjustment

Emotional and psycho-social adjustment difficulties are common in epilepsy as in many other chronic diseases Disturbances occur mainly at three levels patient family and society

Patient An epileptic patient often has a brain damage or dysfunction and subsequently *a tendency to affect lability and decreased* tolerance of conflicts (67) The physical, neurological and mental state of the patient is significantly related to the social prognosis (32, 338) The psychological maladaptation is often the main handicap in epilepsy The seizures themselves, which cannot be foreseen or controlled, understandably make the pa*tient feel* insecure and helpless, but it is often the very fear of seizures that has an even more damaging effect (273) A fear of sudden death may also be combined (252) The emotional adaptation of an individual may also be related to the social status, although opinions on epileptics belonging as a group to a special social stratum are contradictory (8, 116 272)

Neither criminality (8 175) nor sexual problems (31 84) occur more prevalently in epileptics than in the average population. However a slightly higher prevalence of epilepsy in prisoners compared to the average population was found by Gunn (114) Epileptic automatisms are not the cause of com*mitting crimes* (118)

Family The influence of home and family is stressed by many authors. Broken homes, inconsistent discipline and neurotic parents (31 271 309) overprotection or on the contrary rejection (307) asocial family or family history of psychopathy (84 271) and in particular an impaired mother-child relationship (16 115 252) may greatly affect the emotional development and social adaptation of epileptics and even provoke seizures (304) The same is brought about by chronic conditions of tension in the family atmosphere (221) which must be taken into account in the treatment (203 217) On the other hand, seizures may become a psychological necessity to the patient as a weapon of defence and to the family as a motivation of continuous overprotection (309) An unconsciously negative attitude towards therapeutic measures is found particularly in patients whose mothers are physicians, nurses or kindergarten or *school teachers* (233 328) *The disturbances* may be increased by the introduction of a newborn baby into the home (180 181) when the patient feels jealous, insufficient and rejected.

Parental attitudes involving strictness in upbringing practices are significantly correlated with social development (127) Based on the study of the parents of 160 epileptic children Hauck (129) came to the conclusion that the following environmental factors contribute to an unfavourable prognosis for seizures and personality development authoritarianism and autocracy in child rearing, the practice of corporal punishment and a clear cut improvement or decline in social conditions.

Spiel and Strotzka (300) stressed the significance of psychogenic factors and the favourable effect of changing the milieu.

Society The reserved public attitude towards epilepsy has a long history as early as 2080 BC the orders in the code of Hammurabi prohibited marriage and the validity of testimony in court of an epileptic, thus reflecting prejudices even at that time. The public attitude is in much the same to-day even though the situation is improving (39) Surveys of attitudes in USA (39) and West Germany (128) showed that opinions were divided on questions as to whether epileptics should be employed like others (76 per cent answered yes in USA) or whether people would not object to a child with epilepsy playing with their own child (81 per cent answered yes in USA and 63 per cent in Germany)

The effect of public prejudice on seizures and behaviour of patients is considerable (130 207) although the parental influence is even stronger (14) Sociologically the position of epileptics is that of a deviating minority group (130) However negative attitudes towards epileptics are even stronger than towards other handicapped persons (14) The basic mechanism causing this attitude could be "a fear of sudden loss of physical and emotional control 'the man with epilepsy is feared and hated because he does what we are afraid we will do ourselves" (14) This deep-rooted fear is not easily eradicated.

Institutionalization

There are few studies on the prevalence rate of institutionalization of epileptics. In 1960, 7 per cent of epileptics in England were institutionalized, according to the study of Pond and Bidwell (279) Ten years later the respective figure was in Norway 10 per cent (137) and in West Germany 11 per cent (164) The differences in figures may depend on the fact that the need for inpatient care is not the same as the prevalence rate of institutionalization. The needs are greatly dependent on national economical resources, health service systems *etc.* Only 2—3 per cent of cases are chronically or permanently taken care of in institutions (164 338)

The reasons for institutionalization for long term care were in the series of 75 patients with known reasons (164) dementia in 11 and behaviour disorders independent of seizures in 3 cases. For short term care the reasons were post-ictal exitement states in 18 cases and acute or drug induced dysphories or psychotic episodes in 14 cases.

Rodin (280) extensively analysed his material of 57 inpatient epileptics contrasted to 162 patients who were referred from the community The author concluded that patients in institutions were mainly cases with intense seizures with an early onset and refractory to treatment cases with cerebral injuries with early onset and a marked intelligence deficit and fewer cases with no marked seizures or mental retardation but instead, severe behavioural disturbances not tolerated by the environment.

Brain damage — common in institutionalized patients — is also reflected in EEG as predominantly slow background activity and frequent local finding (18, 285)

Different types of epilepsy

Partial cortical epilepsy The incidence of mental changes is essentially lower in partial cortical than in psychomotor epilepsy (16 305) because the limbic system is not affected. No prognostic implications could be made from results of the clinical examination and investigations of Ulrich (321)

Psychomotor epilepsy As Ounsted *et al.* (260) pointed out there is a prevailing opinion that an intelligence deficit is one of the common

111 223 296 322) others found increased hyperkinesis (258) exacerbated psychiatric symptomatology while controlling seizures, mental deterioration and folate deficiency (253) or even a state resembling organic psychosyndrome (301) On the other hand the common sedative effect of anticonvulsants may be good for erethic and restless patients (87)

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Patient An epileptic patient often has a brain damage or dysfunction and subsequently a tendency to affect lability and decreased tolerance of conflicts (87) The physical, neurological and mental state of the patient is significantly related to the social prognosis (32, 338) The psychological maladaptation is often the main handicap in epilepsy The seizures themselves, which cannot be foreseen or controlled understandably make the patient feel insecure and helpless, but it is often the very fear of seizures that has an even more damaging effect (273) A fear of sudden death may also be combined (259) The emotional adaptation of an individual may also be related to the social status, although opinions on epileptics belonging as a group to a special social stratum are contradictory (8, 116 272)

Neither criminality (8 175) nor sexual problems (31 84) occur more prevalently in epileptics than in the average population. However a slightly higher prevalence of epilepsy in prisoners compared to the average population was found by Gunn (117) Epileptic automatisms are not the cause of committing crimes (118)

Family The influence of home and family is stressed by many authors. Broken homes, inconsistent discipline and neurotic parents (31 271 309) overprotection or on the contrary rejection (307) asocial family or family history of psychopathy (84 271) and in particular an impaired mother-child relationship (16 115 259) may greatly affect the emotional development and social adaptation of epileptics and even provoke seizures (304) The same is brought about by chronic conditions of tension in the family atmosphere (221) which must be taken into account in the treatment (303 214) On the other hand, seizures may become a psychological necessity to the patient as a weapon of defence and to the family as a motivation of continuous overprotection (309) An unconsciously negative attitude towards therapeutic measures is found particularly in patients whose mothers are physicians, nurses or kindergarten or school teachers (233 328) The disturbances may be increased by the introduction of a newborn baby into the home (170 181) when the patient feels jealous, insufficient and rejected.

Parental attitudes involving strictness in upbringing practices are significantly correlated with social development (127) Based on the study of the parents of 160 epileptic children Hauck (129) came to the conclusion that the following environmental factors contribute to an unfavourable prognosis for seizures and personality development authoritarianism and autocracy in child rearing, the practice of corporal punishment and a clear cut improvement or decline in social conditions.

scores have been obtained after seizures have stopped (261) Additionally it should not be forgotten that the results may have been affected due to varying conceptions on the significance of the term PM which may have included akinetic myoclonic and other minor seizures.

Progressive mental retardation has been demonstrated after frequent PM statuses (217 220)

Character disorders are uncommon regardless of whether aetiology is genuine or symptomatic (24 87) Instead, neurotic disorders predominate (24, 102, 271 325) Breath-holding spells were found in 8 per cent in infancy Twenty six per cent of 33 cases (325) had neurotic symptoms which commonly occurred as nightmares, nail-biting, thumb-sucking *etc.* Janz (163) found that disorders are similar (271) to those in awakening epilepsy School difficulties are often connected (24, 163)

Grand mal. The intelligence level is lowered by occurrence in itself (331) early onset (339) and high frequency (194) of GM seizures. Higher scores are found in awakening than in sleep epilepsy (163) The occurrence of GM or mixed seizures is in correlation with poor school performance (203)

Behavioural problems and personality changes are rarer with a late onset of GM (87) and in sleep epilepsy compared to the awakening type (217) Idiopathic GM like other genuine types, tends to be associated with enechetic changes (87) Pond (271) found temper tantrums and GM related to each other Blumer (24) claimed that behavioural and personality aberrations are the most frequent in GM epilepsy Janz (163) analysed character differences between awakening and sleep GM epilepsies. He felt that patients with awakening epilepsy are light minded, suggestible easily lead, hot-tempered and infantile while those with sleep epilepsy are pedantic, persistent industrious and hypochondriac.

Infantile spasms There is general consensus that the intelligence level is on the average lowest in infantile spasms. No more than 2 to 19 per cent of cases have an IQ over 85 (See *Table* 4) High frequency and severity of attacks contribute to a bad outcome, which

Tabl 4. Percentages f different clinical aspects and prognosis given in the literature for infantile spasms

Author(s)	No of patients	Minimum period of follow-up (yr)	ACTH, steroids	Types of epilepsy other than inf spasms	Total recovery from seizures	Normal EEG	Mentally normal (IQ 85 or more)	Cases of death	Completely healthy (no fits, no EEG, mental or motor abnormalities)
Alvin *et al.* 1966 (9)	42	2	yes	26	43	31	19		10
Bower and Jeavons 1959 (25)	22	1	yes		5	5	5	9	5
Bray 1963 (28)	10	4	yes				10	10	10
Chevrie *et al.* 1968 (48)	58	1	yes	12			13	3	13
Dumermuth 1961 (72)	26	1	yes	10	23			10	8
Friedman and Pampiglione 1971 (90)	103	7	yes				13	26	
Gibbs *et al.* 1954 (101)	60	3	no	33	54	10			10
Harris 1964 (125)	75	1	yes			8	8		8
Janz and Matthes 1955 (166)	27	15	no	30	11			52	
Jeavons and Bower 1961 (167)	30	2	no	33		41	0	13	0
Jeavons and Bower 1964 (168)	112	¼	yes	50	13	11	13	17	11
Livingston *et al.* 1958 (218)	022	3	no		31			4	2
Schmidt 1964 (288)	32	¼	yes		6?	22	12		12

is not relieved by recovery from seizures (163)

Zellweger (336) found a better prognosis in males *quoad vitam et intelligentiam*. Chevrie *et al.* (48) agreed as to mental prognosis but pointed out that all males in their series had a cryptogenic aetiology which may have been of more prognostical significance than sex. Hereditary factors such as seizures, psychoses and mental retardation in relatives are of no prognostic value as to mental development or life expectancy (336). A lack of seizure history in the family is a good prognostic sign according to Jeavons and Bower (168).

An outlook for the future intelligence level can often be given in a few months after the onset of spasms (169). The mental prognosis is more favourable when seizures only continue for short periods (44) and are symmetrical (?97). The prognosis for both mental and personality development is also better when the age at the onset of seizures is more than one year (87).

Akinetic myoclonic epilepsy. Mental retardation is one of the commonest complications also in this type of epilepsy: at least 50 per cent of cases will be mentally defective in the course of the disease (102). In Kruse's (194) sample of 8? cases, ?0 per cent were of normal intelligence and 27 per cent were borderline cases, while 53 per cent had an inferior mentality (with grave to profound retardation in half of them). Personality disorder was associated with mental retardation in 33 per cent, while personality changes without an intelligence deficit occurred in 6 per cent. One year after the last seizure 35 per cent had defective intelligence and 8 per cent behavioural problems.

D. MORTALITY

Livingston strongly emphasized in 1963 (216) and again in 1972 (217) that "there is no reason why a person with epilepsy should not live as long as he would if he did not have epilepsy" with the exception of myoclonic epilepsy and provided that patients are under adequate medical control and afforded social services and guidance. He referred to the high mortality rates of many earlier series derived from institutions which therefore were not representative of the average population. He also stressed that these studies were mostly carried out at a time when opinions, methodology, findings and implications differed from the modern ones and when bromide and phenemal were the only anticonvulsant drugs. He also stated that epilepsy should not be taken as a global concept but instead divided into specific types, because the different subtypes greatly differ in regard to prognosis. Schwade and Otto (?91) reached the same conclusion as Livingston that mortality is not higher in epileptics.

However there are studies on non-institutionalized patients presenting such mortality rates as 6 to 17 per cent in childhood (31, 184, 185) which must be essentially higher than those in the average population.

As to different causes of death in epilepsy a difference can be made between causes directly due to and those more or less attributed to, epilepsy.

Deaths due to status epilepticus account for 5—1? per cent of all causes in reports from recent years (149, 165, 184, 192, 206, 303). No less than 47 per cent of Bridge's (31) paediatric cases had died of an epileptic status after the average follow-up of six years.

Causes that can be related to epilepsy are often difficult to ascertain and there is a wide variety of figures in this regard. In the mainly paediatric samples of Bridge (31) and Lennox (206) such causes were found in 13 and 15 per cent respectively. These causes include accidents like drowning, which occurs in approx. 10 per cent (184, 19?, 206).

Pneumonia and other respiratory infections with a fatal outcome occur in 27—?8 per cent

(185 19?) and sudden death in 13—17 per cent (192, 249) Opinions on the contributory role of mental retardation in mortality are controversial (8, 138, 139) but institutionalized patients are regarded to be at a higher risk for death than outpatients (217)

The mortality rate in different types of epilepsy is variable. Janz and Matthes (166) were able to follow 27 cases with infantile spasms for 25 years. They found that the mortality rate after that period of time was 4? per cent. After the follow up of the same duration, four out of 33 patients with pure PM, or 12 per cent, had died (163) It is probable that the mortality rates of other types fall between the percentages of these two, prognostically extreme types.

Female mortality was higher than that of males in patients with infantile spasms in the sample of Jeavons *et al* (169)

E. SUMMARY OF THE LITERATURE

Prevalence and incidence There seems to be general agreement that the prevalence rate of epilepsy at the age of 0—?0 years varies between 3 and 5 per 1000 The average annual incidence of new cases is more variable figures offered are 37—67 per 100 000 The differences between figures probably depend on how accurately the criteria for an epidemiological investigation have been fulfilled as to the definition of epilepsy and limitation of age, time period of sample collection and the geographical region.

Prognosis for seizures. No uniform conclusions on the seizure prognosis can be drawn on the basis of the literature. There are, however some features common to many reports. Normal mental and motor development and normal EEG in cases with seizures are generally considered to have a good outcome. On the other hand, if an early — often pro- or perinatal — brain damage develops, it is also early associated with gross developmental and neurological abnormalities and seizures which are refractory to treatment Highly pathological EEG does not inevitably signify a bad prognosis, with the exception of some specific epileptic patterns such as hypsarrhythmia.

No actual differences in final seizure freedom exist between different types of epilepsy This is especially due to the fact that even seizures which are prognostically favourable are often combined with other persistent seizures.

Prognosis for intelligence Although a normal intelligence level is generally reported to be present in a third to one half of cases or more the rather uniform conception seems to prevail that in cases with symptomatic epilepsy an initially low intelligence level will further deteriorate in the course of years. However remarkable individual variations do occur and even a rise in the level is possible in favourable circumstances. The seizures themselves, if not long-durating or statuses, are seldom responsible for a gross decline in intelligence.

Prognosis for schooling School achievement is self-evidently correlated to intellectual capacity but school difficulties are also more frequently found in epileptic patients with normal intelligence than in the average population. It has been suggested that epileptic patients have a higher potential level than their performance would imply but that they avoid developing themselves for complicated psychic reasons.

Prognosis for employment Unemployment is more frequent in epileptics than in others, this being largely due to prejudices felt against them. Investigations of epileptic workers in employment have revealed that their work batch is better and sickness absenteeism less frequent than the average, provided the patients are under regular medical treatment and continuous social

support and care. Accidents in industry are no more than in the average population. Different seizure aspects have little or no significance for employability.

Prognosis for behaviour. Although behavioural disturbances are not infrequent in epileptics, there is no evidence that a specific disturbed behavioural pattern or "epileptic personality" should exist. Behaviour interpreted as specifically epileptic is associated with organic brain damage, which can be implicated from neurological abnormalities and "organic" features in a psychological examination. The non-existence of brain damage prognosticates good school achievement and a normal behavioural pattern in later life. The role of anticonvulsant medication in behaviour is controversial. Perhaps the determination of blood concentrations of antiepileptics will elucidate this question.

Psycho-social adjustment. A feeling of dissimilarity of the patient and his parents, a fear of seizures at any time or even fear of death tend to increase tensions particularly in the home, and tension, for its part, increases the risk of seizures. Overprotection, authoritarianism and an asocial home environment make it further uneasy to adapt oneself in the milieu. According to Gallup examinations in different countries, misunderstanding and false conceptions are gradually decreasing among people and a more favourable environment is being created to lessen the difficulties in adjusting to the society.

Institutionalization. Both intractable seizures and grossly abnormal behaviour — often due to early brain damage — are the main reasons for institutionalization. One tenth of epileptics is in need of this care, but no more than —3 per cent is chronically or permanently institutionalized.

Mortality. It is probable that patients with epilepsy have an increased risk of early death. Rates of 16—17 per cent have been presented which are essentially higher than the average. Status epilepticus is still responsible for death in 5—12 per cent of cases. The commonest cause of death is respiratory tract infection, frequently of a secondary character.

III OBJECTS OF THE PRESENT STUDY

The objects of the present study were to examine

1. prevalence and incidence of epilepsy in children 0—15 years of age in South western Finland,
2. prognosis for final recovery from seizures and factors influencing prognosis,
3. prognosis for intelligence and school achievement,
4. prognosis for employability and other factors influencing the earning of one's living,
5. prognosis for behaviour and psyho-social adjustment,
6. need for institutional care,
7. prognosis for survival.

IV PRESENT PATIENT SERIES AND METHODS

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A. MEDICO-GEOGRAPHIC BACKGROUND

The TUCH region is situated in South western Finland (*Fig* 1) which is one of the most prosperous and advanced parts of the country The population of the region numbered 400 000 inhabitants at the end of 1963 and 450 000 (of which one third resided in the city of Turku) in 1970 which accounts for one tenth of the total population of Finland

The Department of Paediatrics, TUCH is the centre for all child care activities in the region. In addition there are three other hospitals with paediatric department, and a central institution for mentally retarded.

Patients enter hospital partly as emergency cases, partly remitted by other hospitals, community health officers, private practitioners and particularly by doctors in child welfare centres. At these centres, which for half a century have as an essential part belonged and still do belong to the public health system in Finland, all children of pre-school age (below 7) attend at regular intervals. Health nurses from the centres visit homes regularly and as family nurses" they ... also often the first to be called when a ch... is taken ill. Similarly doctors in welf... centres usually also active as family doct... and community health officers have a g... knowledge of the population in the distr... In the two urban communities, the welf... centre doctors are usually paediatricians.

The welfare centre system covers the wh... country and its services are very activ... utilized by the population. Thus, the netw... of centres forms an important and effect... system for health control and screening a... prevention of illnesses. However the Finn... publich health policy has in the post w... period been very hospital minded; the tre... ment of sick people has been greatly c... centrated in the hospital outpatient and ... patient departments.

It has for a long time been our policy ... hospitalize all patients with recurrent s... zures of any type This has not been diffic... when considering the circumstances stat... above. That this practice has actually be... followed was confirmed by the answers in ... questionnaire directed to the practitioners ... the region who were engaged in child c... in 1961—64

B. COLLECTION OF THE SERIES

To collect all the patients who fulfilled t... given criteria for age occurrence of recurre... seizures at the given time period and pla... of permanent residence the following doc...

III OBJECTS OF THE PRESENT STUDY

The objects of the present study were to examine

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5. prognosis for behaviour and psyho-social adjustment,
6. need for institutional care,
7. prognosis for survival.

cepted when motor symptoms or disturbed consciousness or both were involved.

The following exclusions were made

1) Seizures occurring within the first week of life only
2) Seizures of occasional situational character only such as
   — breath holding spells
   — febrile convulsions
   — C.N.S infections
   — temporary disturbance of metabolic balance such as hypoglycaemia hypocalcaemia
   — hysterical and other psychogenic fits
   — attacks occurring within the first week after an acute head trauma only
   — other fits of immediate external cause
3) Paroxysms of headache abdominal pain, vertigo or other paroxysmal phenomena without motor symptoms or disturbed consciousness
4) Symptomatic epilepsies such as those connected with
   — progressive degenerative disease with cerebral involvement, *e g* phenylketonuria
   — space occupying intracranial processes, *e g* cerebral tumour phakomatoses
   — other symptomatic epileptogenic causes, *e g* intracranial catheter for C.N.S. shunt *etc*

Altogether 43_ patients with at least one defined epileptic seizure were found. The vast majority of them had been hospitalized at least once for seizures. When 84 cases with less than three seizures, 100 nonhospitalized cases, and three cases who could not be traced were excluded, there remained 24_ cases who were hospitalized in 1961—1964 and formed the final sample to be more closely analysed for prognostical purposes. Henceforth this final sample will be referred to as the present series or sample.

C. CONTROL SERIES

Several control series were used to compare statistically different aspects of the present series to the average population. As *Fig* 1 shows the regions of control populations mostly cover the TUCH region rather precisely The border districts do not essentially differ demographically socio-economically or in other respects.

The main part of the data was derived from the Finnish census of 31. 12. 1970 (*Table* 6)

Table 6. Different control samples and respective regions

Variables	Age group (in yrs.)	No. of persons	Region
Birth order	0—14 0—19 0—?1	2?5.710	CTP
Height	2—20	17.531	"Miniature Finland"
Weight	?—20	17.510	
Head circumference	0—14	2.?09	"
Age at menarche	10—20	5.399	"
Marital status	20 22—24	31.040	V-SRPA
School education	average population	391.227	"
No of rooms per capita		689 445	CTP
Facilities of conventional dwellings		1.068.022	WHC
Tenure status of conventional dwellings		140.416	V-SRPA
Distribution of occupations	"	2.033.208	WHC
Degree of education		181.516	CTP

Data used were given for Varsinais-Suomi Regional Planning Area (V-SRPA) County of Turku and Pori (CPT) or for the whole country (WCH) The data are preliminary but they do not differ from the final results by more than ± 0.5 per cent according to the Central Statistical Office of Finland.

Another useful source of knowledge was the project of "Healthy child studies drawn in Finland since the 1960's (36, 318) from statistically relevantly chosen districts or "miniature Finland This was chiefly employed for a comparison of physical growth and maturity

No statistically significant differences exist between the various populations used, with the possible exception of the whole country where the socio-economic status is on the average lower than in the TUCH region.

Distribution of occupations in the present series was compared to that of the whole country by the use of data collected by Rauhala in his works "The social stratification of the Finnish society" (277) and "Quantitative strength of social strata in Finnish society" (278)

D. METHODS OF EXAMINATION

All the patients in the present series had been hospitalized earlier for clinical neurological and developmental examination and investigations which included routine clinical chemical, haematological, skull X-ray EEG and psychological analyses and studies. In selected cases, air encephalography cerebral angiography various metabolic, endocrine and other complementary investigations were performed.

The mean age at the beginning of the follow-up was 56±19 months and at the last examination 186±61 months. The patients were followed for the minimum period of 84 months (from the end of 1964 to the end of 1971, see *Table* 7) The longest follow-up was

Table 7 Duration of follow up of the patients

Duration (in years)	No of patients	Percentage
< 7	7	2.9
7 — 8	39	16.0
8 — 9	31	12.6
9 — 10	42	17.1
10 — 11	38	15.5
11 — 12	26	10.6
12 — 13	18	7.3
13 — 14	10	3.7
14 — 15	7	2.9
≥ 15	28	11.4
Total	245	100

264 months and the mean was 10 years (180± 42 months) Seven patients died, however during the follow-up period, after 70 70 69 43, 40, 27 and 27 months, respectively

On examination at the end of the follow-up, a detailed previous history of hereditary obstetrical and developmental factors, seizures, and other diseases was taken. Data were obtained from earlier records and notes of hospitals, institutions and welfare centres, from interviews with patients, their parents, relatives and, in certain cases, with health nurses, teachers and employers.

When taking the previous history the following interpretations were used on different concepts.

Toxaemia of pregnancy was considered to have been present when the criteria given by Dieckmann (65) were fulfilled. In brief these include onset after twenty four weeks and blood pressure of 140/100 or more in at least two successive measurements, or proteinuria or both.

Imminent abortion was manifested as a bloody discharge during the first three months of pregnancy or as a shortened uterine neck or opened internal uterine os on vaginal examination.

Babies born two weeks or more prior to the expected date and with a birth weight below 2500 g were termed premature.

author's own experience were taken into account by adding 10 per cent to the defined border

Small for date were newborns with a birth weight more than two standard deviations below the mean intrauterine weights matched to weeks of pregnancy obtained in the study of 29,516 children at Helsinki welfare centres (37)

Postmature were newborn infants born two weeks or more after the expected date and with typical clinical signs in skin and typical vigilant behaviour

When evaluating the psychomotor development, the Denver Developmental Screening Test (85) revised by taking even borderline cases as normals (86) was used. The border between normal and abnormal was defined as the age where 90 per cent of presumably normal children performed different test items in the first format of Frankenburg and Dodds (85) The revision and the present author's experience were taken into account by adding 10 per cent to the defined border

Classification of different intelligence levels was performed by the use of numbers 310—314 in the Finnish translation of the International Classification of Diseases and Causes of Death 1969 (153) accepted by World Health Organization 1967 with the exception that numbers 310 (mental deficiency) and 311 (mild mental retardation) were in some connections united.

Clinical neurological examination was made personally by the present author in altogether 328 cases, 83 of which were rejected on different grounds. EEG air studies and other complementary investigations were made when necessary at the end of the follow-up period.

EEG records of the patients had been obtained by the use of the 10—20" international system of electrode placement (collodion) the 16 channel (Type 55) Kaiser and since 1966 the 16 channel Mingograph EEG Universal (Model EM 160/16 A, Elema Schönander AB Sweden) EEG machines. The minimum recording of 30 minutes with both unipolar and bipolar derivations, during wakefulness and mostly also during sleep (at times induced) and with photic stimulation and hyperventilation (1—3 minutes) were all employed. All aspects of the records had been interpreted by the two neurophysiologists) themselves or by other physicians of the EEG department under their immediate control.

The neurophysiologist's opinion on the records was transformed to figures for data analysis according to the record analysis schedule, presented in *Appendix* II The localization of EEG findings was coded by the use of a three-numbered figure, the numbers corresponding to the sites of electrodes. With the aid of these three-numbered figures it was possible to show the existence of generalized findings and to localize focal ones in both fronto-occipital and right-left direction. Accentuated lateralization could also be demonstrated.

In data analysis, the initial and mean follow up EEGs were used. Only EEG variables with increasing or decreasing degree of a feature could be considered in the mean follow up EEGs.

Psychological tests most commonly used were the following Bender Benton, Cattell Good-enough's Draw-a-man, Rorschach, Terman Merrill Lehtovaara (The Finnish sample examination and application of Terman Merrill) WAIS and WISC tests. These were given by several clinical psychologists in the Departments of Paediatrics, Turku and Helsinki Universities, the special hospital Children's Castle and several central institutions for mentally retarded.

Statistical analyses were performed by the use of UNIVAC 1108 and in part IBM 1130

) Assoc. Prof Pentti Vallesla M.D and Doc. Heikki Lang, M.D

data machines in the Institute of Applied Mathematics, Turku University

At first, straight and frequency distributions were performed. A number of applicable variables were then tested with Pearson's product moment correlation test where missing data were omitted ("missing data" intercorrelation)

Other tests used were Student's t-test, analysis of variance test for equality of two hypothetical frequencies (on all these, see 123) and Chi Square test (See 293)

Variables used in different tests are shown in *Appendix* I. To avoid too small classes on the Chi Square test, the classes of the following variables were partly combined school education, frequency maximum of seizures, occurrence of seizures during the latest 12 months, final recovery from seizures, temporary recovery from seizures, intelligence level and number of different seizure types. Moreover partial cortical and psychomotor seizures, as well as infantile spasms and akinetic-myoclonic seizures, were combined respectively

The following limits of statistical significance were used:

$0.01 < p \leq 0.05$ slightly significant
$0.001 < p \leq 0.01$ significant
$p \leq 0.001$ highly significant

V RESULTS

A. PREVALENCE AND INCIDENCE

Prevalence The average population of the age group 0—15 years in the TUCH region numbered 108019 on January 1 1965 according to the Central Statistical Office of Finland On this prevalence day" 348 out of this population had had recurrent seizures during the latest four years. The average prevalence rate of epilepsy is thus 3.2 per 1000 in this age group. *Table* 8 shows the variety of age-matched rates for the two sexes, total and cumulative total rates. The figure for males aged 0—15 is 3.6 per 1000 and for females 2.8 per 1000

When cases with one or two typical epileptic seizures are included, the total rate is 4.0 per 1000 The distribution is rather even, with the exception of a small rise at puberty and low incidence in the first year of life. The majority of patients are males.

Table 8. Average prevalence of epilepsy per 1000 for different age groups on 1. 1 1965 (n = 348)

Age (in yrs)	Male	Female	Total	Cumulative total
< 1	0.6	0.9	0.8	
1	3.0	1.9	2.4	1.6
2	3.2	3.6	3.4	2.1
3	3.0	3.0	3.3	3.3
4	5.1	2.3	3.7	3.4
5	4.3	1.7	3.1	3.0
6	2.3	3.5	2.9	3.3
	_1	1.9	2.0	3.1
8	4.8	3.0	3.9	3.2
9	3.0	4.0	3.8	3.3
10	4.0	3.5	3.8	3.1
11	3.2	3.5	3.4	3.4
1	5_	2.2	3.7	3.4
13	3.6	3.5	3.6	3.4
14	3.8	4.6	4.2	3.5
15	4.3	2.0	3.2	3.2
0— 5	3.3	2.2	2.8	
6—10	3.4	3.2	3.3	
11—15	4.1	3_	3.6	
0—15	3.6	_8	3.2	

Table 9 Average annual incidence of epilepsy per 1000 (n = 397)

Age (in yrs)	Male	Female	Total	Cumulative total
< 1	1.10	0.73	0.9?	
1	0.6?	0.50	0.50	0.?0
2	0.53	0.29	0.41	0.64
3	0.20	0.20	0.21	0.55
4	0.20	0.11	0.15	0.47
5	0.16	0.20	0.18	0.43
6	0.29	0.17	0.24	0.39
?	0.2?	0.19	0.23	0.37
8	0.13	0.18	0.15	0.35
9	0.28	0.25	0.2?	0.34
10	0.25	0.14	0.19	0.32
11	0.10	0.1_	0.11	0.30
12	0.18	0.16	0.17	0.29
13	0.07	0.00	0.08	0.27
14	0.10	0.04	0.07	0.26
15	0.00	0.05	0.07	0.25
0— 5	0.48	0.35	0.42	
6—10	0.24	0.19	0.21	
11—15	0.11	0.09	0.09	
0—15	0.28	0.21	0.25	

Incidence The average annual incidence rate of epilepsy is shown in *Table* 9 The rate for

Table 11. Birth order of the patients compared to the total number of children in the patients' families

Birth order	Patient			Youngest child		
	Male	Female	Total (& percentage)	Male	Female	Total (& percentage)
1st	46	42	88 (36.2)	13	15	28 (11.5)
2nd	44	30	74 (30.3)	41	31	7? (29.5)
3rd	17	24	41 (16.8)	29	26	55 (22.5)
4th	13	7	20 (8.2)	17	21	38 (15.6)
5th	7	5	12 (4.9)	18	8	26 (10.7)
6th	3	2	5 (2.0)	8	6	14 (5.7)
7th	1	1	2 (0.8)	4	3	7 (2.9)
8th	2		2 (0.8)	2	1	3 (1.2)
9th or more				1		1 (0.4)
Total	133	111	44 (100)	133	111	244 (100)

cases aged 0—15 is 0.28 per 1000 for males and 0.21 for females. As can be seen, the incidence rate decreases evenly in both cumulative figures and five-year groups.

B. DEMOGRAPHIC AND MEDICAL DATA

The present series consists of 134 males (54.7 per cent) and 111 females (45.3 per cent) altogether 245 patients. Compared to the average population of the whole country 0—14 years of age (570.533 males and 547.977 females) the male female relationship of 1.22 in the present series is higher than the 1.04 figure for the total population. The age distribution of the two sexes is shown in *Table* 10. The birth order compared to the total number of children in the patients families is presented in *Table* 11. Two thirds of the patients are first or second children, the mean birth

Table 10. Age at onset of epilepsy in the two sexes

Age at onset (in yrs)	Male	Female	Total	Percentage	Cumulative percentage
< 1	35	33	68	27.9	
1— 2	42	29	71	29.2	57.0
3— 4	16	5	21	8.6	65.6
5— 6	16	14	30	12.2	77.9
— 8	6	10	16	6.5	84.5
9—10	8	13	21	8.6	93.0
11—12	8	7	15	6.2	99.2
≥12	2		2	0.8	100
Total	133	111	244	100	

order being 2.3 (2.4 in males and 2.2 in females) The mean size of the patients families is 3.2 children (3.3 in the families of male patients and 3.1 in those of female ones) Thus, the risk for epilepsy is higher in first children The difference is highly significant when tested with the "missing data" inter correlation ($r = 0.758$ $p < 0.001$)

However the distribution of birth orders, when compared to that of the control series for the county of Turku and Pori (*Table* 12) is grossly the same and no statistically significant difference exists.

Tabl 12. Birth order f the patients compared t that f control sample

Birth order	Present series No. of patients (& percentage)	Control series No. of controls (& percentage)
1st	88 (36.2)	4.306 (50.4)
2nd	74 (30.3)	2.713 (31.6)
3rd	41 (16.8)	934 (10.9)
4th	20 (8.2)	343 (4.1)
5th	12 (4.9)	136 (1.6)
6th or more	9 (3.6)	117 (1.4)
Total	244 (100)	8.551 (100)

In *Tables* 13—18, the means of heights, weights and head circumferences in males and females are presented and compared to control series of subjects collected from the statistical "miniature Finland" in the "Healthy child studies (36, 313)

V RESULTS

A. PREVALENCE AND INCIDENCE

Prevalence The average population of the age group 0—15 years in the TUCH region numbered 108010 on January 1 1965 according to the Central Statistical Office of Finland. On this "prevalence day" 348 out of this population had had recurrent seizures during the latest four years. The average prevalence rate of epilepsy is thus 3.2 per 1000 in this age group *Table* 8 shows the variety of age

Table 8. Average prevalence of epilepsy per 1000 for different age groups on 1 1 1965 (n = 348)

Age (in yrs)	Male	Female	Total	Cumulative total
< 1	0.6	0.9	0.8	
1	3.0	1.9	2.4	1.6
	3.2	3.6	3 4	2.1
3	3.0	3.0	3.3	3.3
4	5.1	2.3	3.7	3.4
5	4 3	1.7	3.1	3.0
6	2.3	3.5	2.9	3.3
7	2.1	1.9	2.0	3.1
8	4.8	3.0	3.9	3.2
9	3.6	4.0	3.8	3.3
10	4.0	3.5	3.8	3.1
11	3.2	3.5	3.4	3.4
12	5.2	[illegible]	3.7	3 4
13	3.6	3.5	3.6	3.4
14	3.8	4.0	4.2	3.5
15	4.3	[illegible]	3.2	3.2
0— 5	3.3	2.2	2.8	
6—10	3.4	3.2	3.3	
11—15	4.1	3.2	3.0	
0—15	3.6	2.8	3.2	

matched rates for the two sexes, total and cumulative total rates. The figure for males aged 0—15 is 3.6 per 1000 and for females 2.8 per 1000

When cases with one or two typical epileptic seizures are included, the total rate is 4.0 per 1000 The distribution is rather even, with the exception of a small rise at puberty and low incidence in the first year of life The majority of patients are males.

Table 9 Average annual incidence of epilepsy per 1000 (n = 397)

Age (in yrs)	Male	Female	Total	Cumulative total
< 1	1 10	0 75	0.9?	
1	0.67	0.50	0.50	0.76
2	0.53	0.29	0 41	0.64
3	0.29	0.20	0.21	0.5?
4	0.20	0 11	0.15	0.47
5	0.16	0.20	0.18	0.42
6	0.29	0.17	0.21	0.39
7	0.27	0.19	0.23	0.37
8	0.13	0.18	0.15	0.35
9	0.28	0.25	0.27	0.34
10	0.25	0.14	0.19	0.32
11	0.10	0.1?	0.11	0.30
12	0.18	0.15	0.17	0.29
13	0.07	0 00	0.03	0.27
14	0.10	0.04	0.07	0.26
15	0.09	0.05	0.07	0.25
0— 5	0 48	0.35	0.42	
6—10	0.21	0.19	0.21	
11—15	0.11	0 09	0.09	
0—15	0 28	0.21	0.25	

Incidence The average annual incidence rate of epilepsy is shown in *Table* 9 The rate for

Table 16. Weights means of females on follow-up examination compared to control series (Bäckström & Kantero 1971)

Weight (in kgs) and standard deviations						
	Present series			Control series		
Age (in yrs)	N of patients	Mean	SD	No. of controls	Mean	S D
8	3	30.0	0	923	24.0	3.1
9	4	32.5	15.0	1018	26.8	3.6
10	9	33.9	30.5	834	29.2	4.1
11	7	33.6	20.9	674	32.6	5.6
12	6	38.3	27.5	724	36.3	6.5
13	4	4 .5	35.0	613	41.1	7.6
14	7	45 7	32.7	497	47.0	7.5
15	4	47.5	32.6	396	51.2	7 7
16	9	65.6	33.3	310	54.4	7.6
1	6	56.	28.2	233	55.6	7.2
18	6	63.3	33.7	198	56.6	6.9
19	5	56.0	25.5	155	57.0	6.6
20	2	60.0	0	101	57.1	6.3
21	9	63.3	27.1			
22	12	67.5	24.5			
23	4	00.0	28.2			
24	2	65.0	55 4			
25	1	60.0	—			
Total	100			6678		

Table 17. Head circumference means of males on follow up examination compared to control series (Takkunen 1962)

Head circumference (in cms) and standard deviations						
Age	Present series			Control series		
(in yrs)	patients No. of	Means	SD	No of controls	Means	SD
8	3	52.8	5.6	104	52.6	1.5
9	6	53.2	5.2	106	53.1	1.5
10	~	51.9	4.9	93	53 0	1.7
11	9	51.7	3 6	83	53.3	1.5
1..	11	51.9	5.2	67	53.8	1.6
13	11	54.0	3.1	49	54.2	1.5
14	~	53.1	8.5	29	54.6	2.0
15	6	54.0	3.5			
16	9	55.0	6.5			
17	8	5.1	8.8			
18	8	55.5	8.8			
19	1	56.0	—			
20	4	58.0	0			
21	4	56.0	8.1			
22	5	55.2	5.7			
23	1	56.0	—			
24	6	56.3	2.6			
25	2	58.0	0			
26	1	56.0	—			
Total	110			532		

Table 18. Head circumference means of females on follow up examination compared to control series (Takkunen 1962)

Head circumference (in cms) and standard deviations						
Age (in yrs)	Present series			Control series		
	N of patients	Means	SD	No of controls	Means	SD
8	4	50.5	2.9	121	51.8	1.3
9	4	51.5	0	115	52.1	1.6
10	9	51.3	4.6	103	52.3	1.4
11	7	51.9	2.5	75	52.6	1.7
12	6	52.0	61.1	84	53.4	1.5
13	4	53.5	4.9	65	53.5	1.6
14	7	53.2	5.5	31	54.0	1.8
15	3	50.6	5.0			
16	9	55.4	2.5			
17	6	53.2	7.5			
18	5	54.4	4.2			
19	5	54.8	2.8			
20	2	55.0	3.5			
21	8	55.5	6.8			
22	11	54.7	3.2			
23	4	55.0	2.9			
24	0					
25	1	58.0	—			
Total	95			582		

Table 13. Height means of males on follow up examination compared to control series (Bäckström & Kantero 1971)

	Height means (in cm) and standard deviations					
	Present series			Control series		
Age (in yrs)	No. of patients	Mean	SD	No. of controls	Mean	SD
8	3	155.0	20.6	911	127.0	4.5
9	9	128.9	13.0	1025	131.2	4.9
10	7	131.4	14.6	874	136.3	5.1
11	10	143.0	6.7	821	142.0	5.4
12	11	147.3	10.1	847	147.0	6.2
13	12	153.0	8.0	602	151.7	6.9
14	6	165.0	10.5	513	157.2	6.8
15	5	164.0	23.0	412	16[illegible].0	7.6
16	10	173.0	20.0	270	172.5	7.1
17	8	168.7	17.3	216	173.1	6.0
18	8	176.2	9.2	170	177.2	6.0
19	1	180.0	—	180	177.2	6.7
20	6	178.3	4.1	97	176.0	5.6
21	4	180.0	8.2			
22	6	171.7	.5			
23	2	173.0	7.1			
24	6	166.7	8.2			
25	3	180.0	10.0			
26	1	180.0	—			
Total	118			911		

Table 14. Height means of females on follow-up examination compared to control series (Bäckström & Kantero 1971)

	Height means (in cm) and standard deviation					
	Present series			Control series		
Age (in yrs)	No. of patients	Mean	SD	No. of controls	Means	SD
8	3	123.3	6.8	925	125.0	4.5
9	4	130.0	14.1	1018	130.0	4.9
10	9	141.1	16.9	895	135.2	5.4
11	7	144.3	5.3	675	141.0	6.2
12	6	141.7	11.7	725	147.0	6.6
13	4	157.5	9.6	613	153.2	7.3
14	7	155.[illegible]	14.0	49[illegible]	159.5	6.5
15	4	165.0	6.8	390	162.0	6.3
16	9	160.7	6.0	310	164.5	5.7
17	6	166.7	6.2	233	164.8	5.0
18	6	165.0	13.8	196	165.1	6.0
19	5	168.6	4.5	1[illegible]	165.1	6.0
20	2	165.0	7.1	102	165.1	5.6
21	9	167.8	6.7			
22	12	160.0	10.4			
23	4	172.5	5.0			
24	2	155.0	7.1			
25	1	170	—			
Total	100			6777		

Table 15. Weight means of males on follow up examination compared to control series (Bäckström & Kantero 1971)

Age (in yrs)	Weight (in kgs) and standard deviations					
	Present series			Control series		
	No. of patients	Means	SD	No. of control	Means	SD
8	3	43.3	33.3	910	24.9	2.9
9	9	35.6	31.3	1025	21.9	3.1
10	7	32.0	21.9	874	29.5	3.5
11	10	33.0	20.7	821	32.5	4.3
12	11	40.0	27.7	847	35.7	5.0
13	1[illegible]	45.8	27.5	602	39.3	5.5
14	6	51.7	31.6	513	44.0	7.3
15	5	50.0	35.8	411	51.0	9.0
16	10	57.0	33.7	278	59.2	5.7
17	9	63.3	35.8	210	62.8	8.2
18	8	62.5	27.1	170	65.0	7.9
19	1	60.0	—	192	67.0	8.0
20	6	76.7	35.1	96	67.9	7.8
21	4	70.0	38.3			
22	7	62.9	20.5			
23	1	100.0	—			
24	6	81.7	27.5			
25	2	80.0	0			
26	1	80.0	—			
Total	108			7027		

Table 21. Pre- peri and postnatal course and development of the patients

Course and development	Normal		Abnormal		Total	
	No of patients	Per-centage	No of patients	Per-centage	No of patients	Per-centage
Course of						
pregnancy	154	(65.3)	82	(34.7)	236	(100)
delivery	163	(68.0)	77	(32.0)	240	(100)
Neonatal state	184	(77.7)	53	(22.3)	237	(100)
Postnatal factors	178	(82.8)	37	(17.2)	215	(100)
Psychomotor development						
gross motor	157	(64.2)	88	(35.8)	245	(100)
fine motoradaptive	136	(55.4)	99	(40.6)	244	(100)
language	130	(54.2)	110	(45.8)	240	(100)
personal-social	132	(59.8)	89	(40.2)	221	(100)

Postnatal stage. All the factors that might be a cause of or contributory to the onset of epilepsy were considered as postnatal factors. Such factors included perforating or otherwise defined cranio-cerebral trauma in 14, meningo-encephalitis in 8 and anoxia (e.g. drowning) in 6 cases. Other postnatal factors included proven hypoglycaemia (blood glucose below 30 mg/100 ml) and intoxication.

The probability of the various abnormalities as a cause of epilepsy is presented in *Table* 22.

Table 22. Suggested aetiology of seizures

Aetiology	Probability of an organic cause					
	Unknown	Possible	Probable	Defined	Total (& percentage)	
Unknown	78				78	(31.8)
Hereditary	37				37	(15.1)
Organic		34	39	16	89	(36.3)
Both hereditary and organic	3	15	19	4	41	(16.8)
Total	118	49	58	20	245	(100)

Psychomotor development. Gross motor development was abnormal in 88 cases (*Table* 21). The presenting symptom was spasticity in 41, tetraplegic dystonia in 2 and ataxia hypotonia in 10 cases. Gross motor clumsiness without defined muscle tone abnormality was present in 3? patients. Moreover two cases were late in gross motor milestones but had otherwise normal motor performance ability. Fine motor-adaptive skills were abnormal in 99 cases or 40.6 per cent. Most often there was language disturbance in 110 patients. Personal social development was deviated in 89 cases.

The neurological examination revealed, in addition to the abovementioned developmental deviations, opthalmological abnormalities in 29 cases, facial paresis in 2, unoperated hydrocephalus in 2 and marked microcephalus in 4 cases.

No significant differences were found in Student's test with inequal variances between the present and control series, with the two exceptions, namely that male patients aged 14 were significantly taller and female patients 18 years of age were highly significantly heavier than the respective controls.

Age at menarche of 61 patients were compared to those of 5.399 controls (179) The frequency maximum of menarche is 12—14 years in the present series and 14—16 years in the controls (*Table* 19)

Table 19 Age at menarche in the present series compared to that of control series (Kantero & Widholm 1971)

Age at menarche (in yrs)	Present series		Control series	
	No. of patients	Per-centage	No. of controls	Per-centage
< 11	0		2	0
11 — 12	6	9.8	66	1.2
12 — 13	1	10 0	313	0.4
13 — 14	19	31.[illegible]	[illegible]	1 [illegible]
14 — 15	6	9.8	1288	23.8
15 — 16	11	18.1	1280	23.0
16 — 17	5	8.2	688	12.7
≥ 21	2	3.3	780	14 4
Total	61	100	5399	100

Using the test of equality of two hypothetic frequencies on the basis of two frequencies, the age at menarche was found to be highly significantly higher in the present patients aged 12 or 13 years than in the control subjects who in turn showed a significantly higher representation in ages 14 15 and 17 or more years.

Handedness was known in no more than 27 cases, where it was demonstrable Of these, left-handedness occurred in eight males and one female. Six males were ambidextrous. Twelve were right handed. The deviation from the average is marked but the number of patients is too small to *justify* statistical conclusions for the whole patient series

Family history Neuropsychiatric disorders of distant relatives (including second cousins)

Table 20. Neuropsychiatric disorders in relatives (per cent)

Neuropsychiatric disorder	Paternal side	Maternal side	Both paternal and maternal	In the patient's family
Mental retardation	6.0	5.3		7.3
Motor retardation	2.9	2.0		0.8
Psychic disorders	5.3	4.5	0 4	6.0
Febrile convulsions	0 1	1 0		.6
Recurrent seizures	6.1	6.5	0.8	13.5

outside the patients families (*Table* 20) are somewhat commoner on the paternal than the maternal side In the same table the data on the close relatives, or 490 parents and 785 siblings of the patients, show that grossly every 14th of them has mental retardation or psychic disorder A similar frequency is seen for febrile convulsions. The frequency of recurrent seizures is markedly high in the close relatives 13.5 per cent.

Pre peri- and postnatal stages of the patients were abnormal in 17.2—34 7 per cent of cases (*Table* 21) Toxaemia during pregnancy was found in 37 Infection of any sort in 16 and Imminent abortion in 14 patients.

In 38 cases, there was a "severe delivery — a concept not properly defined but compatible with cases of long lasting (more than 30 minutes) delivery where there was an atonic labour and where Credé's method was employed to expel the foetus In nine a caesarean section was performed due to the foetal distress and in 17 cases for other reasons of conceivable risk for the foetus (abnormal presentation previous history of deliveries *etc.*)
Maturity of newborns. Twenty two were small for date, eleven premature, nine postmature and the rest normal mature babies.
Neonatal state The neonatal state was abnormal due to asphyxia (no cry occurring during the first minute of life and appearance of cyanosis) in 40 and to skull pathology (deformed skull cephalhaematoma, skull fracture) in 13 cases.

Table 28. Amount of local abnormality in EEG records

Amount of local abnormality	No. of EEGs						
	Unknown	One	Some	Fair	Frequent	Persistent	Total
Non-irritative							
persistent irregular delta activity	1			1	20	26	48
intermittent slowing	18	6	49	78	54	22	227
local low-amplitude activity			1	12	6	5	24
Irritative							
spikes	20	10	54	54	96	21	255
sharp waves	8	4	5	63	61	13	206
spike and wave complexes	2	3	1	34	71	23	150
multiple foci or asymmetries				4	8	3	15
asymmetric spike discharges		1	2	2	6		11
Total	49	24	150	248	322	113	936

Table 29. Organic aetiology of seizures compared to abnormality of initial EEG

Abnormality of initial EEG	Organic aetiology				
	Not known	Possible	Probable	Defined	Total
	N of patients (& percentage)				
Normal	9 (9.3)	8 (14.8)	3 (5.5)	1 (5.3)	21 (9.3)
Borderline	12 (12.4)	2 (3.7)	6 (11.0)	1 (5.3)	21 (9.3)
Abnormal	47 (48.5)	20 (37.0)	28 (50.9)	7 (36.8)	102 (45.3)
Markedly abnormal	28 (28.9)	23 (42.6)	18 (32.7)	10 (52.7)	79 (35.1)
Uncertain	1 (1.0)	1 (1.9)			2 (0.9)
Total	97 (100)	54 (100)	55 (100)	19 (100)	225 (100)

Organic aetiology of seizures in relation to EEG is shown by *Table* 29.

PEG or cerebral angiography or both were performed once or several times in 49 cases. Twenty four cases showed no abnormality. A bilateral symmetric brain involvement was present in 16 patients, mainly left-sided in six and mainly right-sided in three cases.

The aetiological significance of the results from the clinical examination and investigations is presented in *Table* 30.

Table 30. The significance of results of examination and investigations related to aetiology

Significance of results	No. of patients	(Percentage)
Not known	60	(25.4)
Not significant	70	(31.8)
Possibly significant	45	(20.5)
Probably significant	34	(15.5)
Definitely significant	15	(6.8)
Total	220	(100)

C. SEIZURE DATA

Occasional seizures occurred in 35 patients or 15 per cent of the whole sample, *Table* 31. Nineteen were febrile convulsions, six were associated with C.N.S. infections and another six with acute head trauma. Hypocalcaemia was the cause in three cases. The rest — 11 cases — included breath holding spells, cerebral haemorrhages, hypoglycaemia, subdural haematomas, and neonatal fits.

Table 31 Occurrence of occasional seizures

Occasional seizure	N of patients	(Percentage)
Febrile convulsions	19	(42.3)
C.N.S. infections	6	(13.3)
After acute head trauma	6	(13.3)
Hypocalcemia	3	(6.7)
Others	11	(24.4)
Total	45	(100)

Epilepsy. *Table* 32 shows the age at the onset of seizures.

In *Table* 33 the single manifestations of seizures are presented. Almost every fifth patient (18.4 per cent) had symptoms for hours or days in advance and nearly half the patients had seizures with aura. Consciousness was disturbed in 95.8 per cent of cases. Complete unconsciousness occurred in 31.3 per cent, a partial loss in 36.2 per cent. Both complete and partial unconsciousness occurred in 28.4 per cent. In addition to a disturbance of consciousness, autonomic (in 83.1 per cent) tonic (in 74.2 per cent) and clonic (67.5 per cent) signs were commonest. Seizure types with post-ictal signs and symptoms were present in 89.9 per cent of the patients.

Status epilepticus (*Table* 34) occurred at least once in 55 patients (23.6 per cent).

Table 32. Age of the patients at onset of epilepsy

Age at onset (in yrs)	N of patients	(Percentage)
< 1	68	(27.9)
1	44	(18.0)
2 — 3	41	(16.7)
4 — 5	10	(.8)
6 — 7	28	(11.5)
8 — 9	20	(8.2)
10 — 11	14	(5.8)
≥12	10	(4.1)
Total	244	(100)

Table 34. Occurrence of grand mal status epilepticus

N of statuses	No. of patients	(Percentage)
None	178	(76.4)
One	22	(9.4)
Two to three	14	(6.1)
More than three	19	(8.1)
Total	233	(100)

Table 33. Seizure manifestations

Seizure manifestation	Not known		No		Yes		Total (& percentage)	
	No of patients (& percentage)		No of patients (& percentage)		N of patients (& percentage)			
Pre-ictal								
Prodromal	151	(61.9)	48	(19.7)	45	(18.4)	244	(100)
P ictal								
Occurrence of aura	64	(26.6)	64	(26.6)	113	(46.8)	241	(100)
Initial objective sign of seizure	9	(3.7)			234	(96.3)	243	(100)
Disturbance of consciousness	5	(2.1)	5	(2.1)	233	(95.8)	243	(100)
Tonic signs	2	(0.4)	36	(15.5)	173	(74.2)	231	(100)
Clonic signs	7	(3.0)	69	(29.5)	158	(67.5)	234	(100)
Adversive movements	41	(44.5)	65	(28.1)	63	(27.4)	140	(100)
Sensory symptoms	86	(41.8)	93	(45.1)	27	(13.1)	206	(100)
Psychic symptoms and signs	99	(42.7)	80	(34.5)	53	(22.8)	232	(100)
Autonomic symptoms and signs	18	(8.2)	19	(8.)	182	(83.1)	219	(100)
Automatisms	22	(9.8)	148	(54.6)	75	(33.6)	245	(100)
Post-ictal	8	(3.7)	18	(7.4)	217	(89.9)	243	(100)

The rhythmic occurrence of seizures was present in two main ways as the sleep-waking cycle (*Table* 35) and cluster occurrence (*Table* 36) Awakening seizures were not considered due to inaccurate previous history in this regard. Seizures occurred in sleep only in 12.7 per cent and in a waking state only in 40 4 per cent. In the two states seizures were present in 46.9 per cent of cases. Cluster occurrence was infrequent no more than 29 cases (13 4 per cent) were found to have such manifestation.

Table 35. Occurrence f sleep-waking cycle

Sleep-waking cycle	N of patients	(Percentage)
In waking state only	92	(40.4)
In sleeping state only	29	(12.7)
In both waking and sleeping stat	107	(46.9)
Total	228	(100)

Table 36. Cluster occurrence of seizures

Cluster occurrence	No. of patients	(Percentage)
Never	188	(86.6)
Infrequent	14	(6.5)
Frequent	15	(6.9)
Total	21	(100)

The adequacy of the medical treatment of seizures (*Table* 37) was judged in accordance with the present accepted principles. Parametres which were taken into consideration, were anticonvulsants employed as compared to seizure types, their daily total and divided doses and way of withdrawal (whether too abrupt or not) Approx. 10 per cent had probably not been adequately treated.

Table 38 shows the relationship between the adequacy of medical therapy and final control of seizures. Final remissions from seizures in seven years or more in adequately (25 4 per cent) possibly inadequately (31 6 per cent) and probably inadequately (22.7 per cent) treated cases do not differ from each other The same holds true when final remission was three or more years (40.2, 52.6 resp 36.3 per cent)

Table 3‾ Adequacy of medical therapy

Adequacy of therapy	N of patients	(Percentage)
Adequate	144	(64.0)
Possibly inadequate	59	(26.2)
Probably inadequat	22	(9.8)
Total	225	(100)

Tabl 38. Adequacy f medical therapy compared to final freedom from seizures

Final recovery from seizures (in yrs)	Adequacy of therapy: Adequate	Possibly inadequate	Probably inadequate
	No of patients (& percentage)	No of patients (& percentage)	No. of patients (& percentage)
No recovery	63 (44.4)	4 (42.0)	13 (59.2)
<1	(4.9)	1 (1.8)	
1—2	8 (5.6)	1 (1.8)	
2—3	7 (4.9)	1 (1.8)	1 (4.5)
3—5	13 (9.2)	7 (12.3)	1 (4.5)
5—7	8 (5.6)	5 (8.7)	2 (9.1)
≥7	36 (25.4)	18 (31.6)	5 (22.7)
Total	142 (100)	57 (100)	22 (100)

On intercorrelation analysis, the only variables which were slightly correlated with adequacy of medical therapy were a short-term result of treatment and an occurrence of irritative paroxysms.

The total duration of seizure illness (*Table* 39) was seven years or more in over half of the cases (57 6 per cent)

Different types of epilepsy Only one type of epilepsy occurred in 168 patients or 68.5 per cent A combination of two types was present in 67 (27 4 per cent) and of three or more types in 10 cases (4 1 per cent) The

Table 40. Seizure frequency of the patients

Frequency	Maximum frequency	Frequency during the latest 12 months
	No of patients (& percentage)	No of patients (& percentage)
None		1[illegible]6 (52.1)
Fewer than one a year	[illegible]0 (8.2)	
One a year	6 (2.4)	18 ([illegible]4)
2—5 year	31 (13.0)	2[illegible] (9.1)
5—10 a year	25 (10.2)	
One a month	9 (3.7)	4 (1)
2—3 a month	21 (9.8)	9 (3.[illegible])
One a week	1 (4.9)	6 (2.5)
More than one a week	115 (46.9)	5 (23.0)
Total	245 (100)	[illegible]42 (100)

Table 4[illegible] Results of treatment

Degree of decrease of seizures	Short term results	Long term results
	No of patients (& percentage)	No of patients (& percentage)
75—100 %	8[illegible] (40.0)	133 (5[illegible].6)
50— 75 %	50 (23.0)	16 (6.9)
0— 50 %	80 ([illegible]7.0)	8[illegible] (35.5)
Total	[illegible]1 (100)	231 (100)

Variables which are in correlation with the seizure maximum are shown in *Table* 48. Highly significantly correlated with a low seizure maximum are the following variables good short term results of treatment, small number of seizures before starting the therapy normal initial EEG occurrence of seizures either at daytime or in sleep small number of seizure types and high intelligence level. The occurrence of irregular occipital rhythmic activity in the follow-up EEGs, cluster occurrence of seizures and completely disturbed consciousness during seizures, are related to high seizure maximum.

The Chi Square test showed that the normal gross motor fine motor and mental state are significantly correlated to the low frequency maximum of seizures.

Table 48. Intercorrelation of variables with frequency maximum of seizures

Variables	r	p
Frequency of seizures during the latest 12 months	.522	0.001
Long term results of treatment	.4[illegible]	0.0[illegible]1
Final remission from seizures	.460	0.001
Short-term results of treatment	.410	0.001
Capacity for work of those occupied	.401	0.001
Pretreatment number of seizures	.39[illegible]	0.001
Duration of seizure illness	.391	0.001
Degree of abnormality in initial EEG	.355	0.001
Sleep-waking cycle	.323	0.001
Degree of abnormality in mean follow up EEGs	.309	0.001
Number of different seizure types	.29[illegible]	0.001
Development of personal independence	.2[illegible]6	0.001
Influence on choosing an occupation	.2[illegible]0	0.001
Intelligence level	.242	0.001
Number of hospitalizations	.230	0.001
Irregular occipital rhythmic activity in mean follow up EEGs	.2[illegible]5	0.01
Ability for inter personal contact	−.23[illegible]	0.01
Main type of activity	.218	0.01
Cluster occurrence of seizures	.203	0.01
Degree of disturbance of consciousness during seizures	.20[illegible]	0.01
Duration of medical therapy	.183	0.01
Duration of phenytoin therapy	.200	0.05
Ability for the activities of daily living	1[illegible]0	0.05
Number of rooms in dwelling	.205	0.05
Tenure status of dwelling	−.164	0.05
Fine motor-adaptive development	.164	0.05
Duration of phenemal therapy	.152	0.05
Temporary remission from seizures	−.145	0.05
Language skills	.140	0.05
Organic aetiology of seizures	.138	0.05

The occurrence of *status epilepticus* — the severest epileptic manifestation — is highly significantly correlated with, for example, the following variables that are present in the beginning of seizure illness (*Table* 49) complete loss of consciousness during seizures, low intelligence level frequent mental retardation in close relatives, poor personal-social development and disability to perform the activities of daily living. A significant correlation exists to poor fine motor-adaptive development.

Table 49 Intercorrelation of variables with occurrence of status epilepticus

Variables		p
Short-term results of treatment	.361	0.001
Influence on choosing an occupation	.359	0.001
Development of personal independence	.338	0.001
Degree of disturbance of consciousness during seizures	.309	0.001
Final remission from seizures	−.309	0.001
Number of hospitalizations	.306	0.001
Main type of activity	.303	0.001
Ability for inter personal contacts	−.291	0.001
Intelligence level	.281	0.001
Frequency of seizures during the latest 12 months	.276	0.001
Sleep-waking cycle	.276	0.001
Long-term results of treatment	.269	0.001
Mental retardation of close relatives	.256	0.001
Ability for the activities of daily living	.238	0.001
Duration of seizures illness	.235	0.001
Personal-social development	.231	0.001
Capacity for work of those occupied	.324	0.01
Need for special education	.301	0.01
Irregular occipital rhythmic activity in mean follow up EEG	.267	0.01
Duration of phenemal therapy	.256	0.01
Language skills	.223	0.01
Number of different seizure types	.214	0.01
Degree of abnormality in mean follow-up EEGs	.212	0.01
Fine motor-adaptive development	.211	0.01
Head circumference of follow-up examination	−.210	0.01
Economically active population	.185	0.05

A *highly significant correlation of* the occurrence of status epilepticus to abnormal fine motor and mental state was found on follow up examination. The correlation is also significant to abnormal gross motor and language state, the occurrence of slow background activity in the mean follow-up EEGs and slightly significant to the occurrence of hyperkinetic syndrome.

Final remission from seizures was in the present sample gained in 27.4 per cent for more than seven years and in 44.0 per cent for more than three years (*Table* 50). As is seen in the same table the final remission may be preceded by quite long-lasting seizure free periods.

Table 50. Remission from seizures

Remission (in yrs)	Temporary	Final
	No. of seizures (& percentage)	No. of seizures (& percentage)
Never	149 (65.4)	106 (44.2)
< 1	15 (6.6)	8 (3.3)
1—2	23 (10.1)	9 (3.[illegible])
2—3	13 (5.7)	11 (4.6)
3—5	16 (7.0)	23 (9.6)
5—7	7 (3.1)	17 (7.1)
≥ 7	5 (2.2)	66 (27.5)
Total	228 (100)	240 (100)

Table 51. Duration of seizure-free period during time of follow-up

Duration of freedom from seizures (in yrs)	No. of patients	(& percentage)
< 1	134	(55.6)
< 2	126	(52.3)
< 3	11	(48.6)
< 5	106	(44.0)
< 7	83	(34.5)
≥	66	(27.4)

Cases with longer seizure free periods become fewer in the course of the follow up period, as is demonstrated in *Table* 51. *Table 52 shows a cross-tabulation of EEG and final* seizure freedom.

In order to demonstrate all the variables that are significantly correlated with the final remission from seizures an intercorrelation was performed. The most significant correlations are presented in *Table* 53. The procedure showed that the following factors have a highly significant ($p < 0.001$) correlation to final recovery long duration of phenemal or other medical treatment, good personal-social, fine motor-adaptive and language development, good language state less

Table 52. Final remission from seizures compared to degree of abnormality in initial EEG

Remission from seizures (in yrs)	Abnormality of EEG				
	Normal	Borderline	Abnormal	Markedly abnormal	Uncertain
	N of patients (& percentage)				
Never	6 (27.3)	5 (25.0)	38 (37.6)	49 (60.5)	
<1	4 (18.2)		3 (3.0)	1 (1.2)	
1—2	2 (9.1)		4 (4.0)	3 (3.7)	
2—3	1 (4.5)	1 (5.0)	5 (5.0)	4 (4.9)	
3—5	3 (13.7)	5 (25.0)	6 (5.9)	7 (8.)	
5—7	1 (4.5)		9 (8.9)	6 (7.4)	
≥7	5 (22.7)	9 (45.0)	36 (35.7)	11 (13.6)	2 (100)
Total	22 (100)	20 (100)	101 (100)	81 (100)	2 (100)

Table 53. Final remission from seizures inter correlated with different variables

Variables	r	p
Frequency of seizures during the latest 12 months	.62	0.001
Long term results of treatment	.746	0.001
Duration of seizure illness	−.741	0.001
Short-term results of treatment	.61	0.001
Duration of phenemal therapy	.4[illegible]4	0.001
Frequency maximum of seizures	−.460	0.001
Influence on choosing an occupation	−.455	0.001
Sleep-waking cycle	−.452	0.001
Number of seizure types	−.440	0.001
Development of personal independence	.390	0.001
Intelligence level	−.373	0.001
Degree of disturbance of consciousness during seizures	.369	0.001
Number of hospitalizations	.335	0.001
Ability for inter personal contacts	.330	0.001
Personal-social development	−.314	0.001
Degree of abnormality in mean follow up EEGs	.311	0.001
Occurrence of status epilepticus	−.300	0.001
Fine motor-adaptive development	.297	0.001
Cluster occurrence of seizures	−.280	0.001
Main type of activity	.270	0.001
Duration of medical therapy	−.258	0.001
Organic aetiology of seizures	.238	0.001
Language development	.230	0.001
Ability for the activities of daily living	.235	0.001
Degree of abnormality in initial EEG	.233	0.001
Occurrence of mental disorders in close relatives	−.235	0.001
Aetiological significance of examination and investigations	−.219	0.01
Economically active population	.138	0.01
Head circumference on follow up examination	.1[illegible]0	0.01
Facilities of dwelling	.172	0.0[illegible]

disturbed consciousness during seizures, normal initial and mean follow up EEGs.

A bad outcome in relation to freedom from seizures was found when there is a high frequency maximum of seizures, seizures occurring in both sleeping and waking states, low intelligence level several types of epilepsy in a patient, frequent epileptic statuses, cluster occurrence of seizures, findings suggestive of an organic cause on clinical examination and different investigations (EEG PEG angiographies) and small head circumference on follow-up examination.

By the use of the Chi Square test a highly significant correlation could be demonstrated between a long final recovery and, on the other hand normal gross motor fine motor and mental state. The occurrence of slow background activity in initial EEG slightly significantly correlated to a persistent seizure illness.

Different types of epilepsy In *Table* 54 a final remission from seizures in patients with different types of epilepsy is presented. As

Table 54. Final recovery from seizures in patients with different types of epilepsy

Type of epilepsy	Recovery in years						
	Never	< 1	1—2	2—3	3—5	5—7	> 7
	No of patients (& percentage)						
Partial cortical	6 (54.6)	2 (18.2)	1 (9.1)		1 (9.1)		1 (9.1)
Psychomotor	57 (45.2)	5 (4.0)	5 (4.0)	9 (7.1)	11 (8.)	9 (7.1)	30 (23.8)
Secondarily generalized	18 (50.0)	3 (8.3)	3 (8.3)	1 (2.8)	4 (11.1)	3 (8.3)	4 (11.1)
Petit mal	6 (50.0)				2 (16.)	2 (16.7)	2 (16.7)
Grand mal	74 (56.9)	3 (2.3)	4 (3.1)	2 (1.5)	7 (5.4)	5 (3.8)	35 (26.9)
Infantile spasms	(70.0)				1 (10.0)	1 (10.0)	1 (10.0)
Akinetic myoclonic	8 (80.0)						2 ([illegible]0.0)
Unclassified	7 (63.6)				1 (9.1)	1 (9.1)	2 (18.[illegible])
Average per patient	(44.0)	(3.3)	(3.)	(4.6)	(9.5)	(7.1)	(2[illegible]4)

may be seen, PM does not differ from other types as to final seizure freedom. As expected, patients with infantile spasms or akinetic myoclonic seizures not infrequently have persistent seizures.

In the Chi Square test, a good result highly significantly correlated to the occurrence of GM seizures ($p < 0.005$) Irritative and non irritative EEG foci are highly significantly found in initial and mean follow up EEGs in patients with partial or secondarily generalized seizures. The correlation is also significant between non irritative bilateral paroxysms in EEG and PM seizures. A slight association exists between the non-occurrence of non irritative foci in the initial EEG and non-irritative bilateral paroxysms in the mean follow up EEG Highly significantly correlated are complete dependence on other persons and the occurrence of infantile spasms or akinetic myoclonic seizures.

Isolated types of fits are highly significantly ($p < 0.005$) correlated, as compared to combined forms, to the following variables freedom from seizures during the latest 1 months, good short term and long-term results of medical therapy low frequency maximum of seizures and long final recovery from seizures. The correlation is significant to a normal intelligence level and non-occurrence of epileptic statuses and slightly significant to daytime or night time seizures only and to the degree of education.

E. SOCIAL PROGNOSIS

Prognosis for intelligence

Not all the patients had been subjected to psychological examinations, which were only performed on clinical grounds, mostly in cases of suspected mental retardation or behavioural disturbances. The mental level of the rest was clinically evaluated by the present author on the basis of both case journals and a clinical examination. In *Table 55* the distribution of

Table 55. Intelligence level f the patients

Intelligence quota	Normal	Deficient	Mental retardation				Total
			Mild	Moderate	Grave	Profound	
	86	85—68	67—52	51—36	35—20	< 20	
Examined	24	30	15	18	7	41	135
Estimated	90	2	1	8	2	5	108
T tal	114	32	16	26	9	46	13
Percentage	(47.3)	(13.1)	(6.6)	(10.8)	(3.7)	(19.1)	(100)

the patients according to intelligence level shows that 42.3 per cent of cases were normal (IQ 86 or more) Cases with an intelligence quota from 85 to 68 numbered 3[illegible] (13.1 per cent) Profound mental retardation was shown in 19.1 per cent In 71 cases, where the intelligence level was followed by a psychologist, 60.6 per cent of the patients showed a deterioration and 36.6 per cent were unchanged (*Table 56*)

Table 56. Change in intelligence during the follow up period

Change in intelligence	No. of patients	(Percentage)
Increasing	2	(2.8)
Decreasing		
5—0 scores	4	(5.6)
more than 0 scores	39	(5[illegible] 0)
Unchanged	26	(36.6)
Total	71	(100)

The "missing data" intercorrelation revealed a highly significant correlation ($p < 0.001$) between the intelligence level and many variables, *Table 57* Some of them can be interpreted as a result of mental retardation and will be taken up later Others are present at the beginning of seizure illness and may aid in prognosticating intelligence development in the future. A good short term result from medical therapy prognosticates a manageable epilepsy and a good intelligence Early age at the onset of seizures, organic cause, occurrence of seizures both in waking and sleeping state occurrence of epileptic statuses, complete loss of consciousness during seizures and the occurrence of mental retardation in relatives are ominous features. Light weight on the initial examination also relates to poor neurological and mental development.

On the Chi Square test, a low intelligence level was highly significantly correlated with abnormal gross motor fine motor and language state and the ocurrence of psycho-neurotic symptoms and hyperkinetic syndrome. A slight correlation also existed to neurotic symptoms.

The duration of phenemal therapy correlated highly significantly ($p < 0.001$) to an abnormal intelligence level on the intercorrelation test ($r = .312$) The correlation of the duration of seizure illness was as strong ($r = .337$) Thus, it is more probable that abnormal intelligence must be ascribed to the duration of seizure illness rather than to the duration of phenemal therapy

Table 57 Intercorrelation of variables with intelligence level

Variables	r	p
Personal-social development	.6[illegible]8	0.001
Ability for the activities of daily living	.810	0.001
Fine motor adaptive development	[illegible]90	0.001
Language development	[illegible]03	0.001
Head circumference on follow up examination	−.563	0.001
Height of patient on follow up examination	409	0.001
Number of hospitalization	409	0.001
Aetiological significance of examination and investigations	456	0.001
Short term results of treatment	444	0.001
Long term results of treatment	.309	0.001
Weight on follow up examination	.396	0.001
Age at onset of recurrent seizures	−.384	0.001
Final remission from seizures	−.373	0.001
Frequency of seizures during the latest 12 months	.370	0.001
Organic aetiology of seizures	.363	0.001
Sleep-waking cycle	.357	0.001
Duration of seizure illness	.337	0.001
Weight on initial examination	.318	0.001
Duration of phenemal treatment	.312	0.001
Age on initial examination	.303	0.001
Occurrence of status epilepticus	.281	0.001
Degree of disturbance of consciousness during seizures	.256	0.001
Frequency maximum of seizures	.[illegible]12	0.001
Age on follow-up examination	190	0.01
Occurrence of mental retardation in relatives	.175	0.05
Cluster occurrence of seizures	102	0.05
Duration of medical treatment	.140	0.05
Tenure status of dwelling	.146	0.1

Table 58. Intelligence level in different types of epilepsy

Type of epilepsy	Normal	Deficient	Mental retardation				Total
			Mild	Moderate	Grave	Profound	
	No. of patients (& percentage)						
Partial cortical	5 (45.4)	? (18.2)		? (18…)		2 (18.2)	11 (100)
Psychomotor	55 (49.1)	18 (16.1)	12 (10)	10 (8.9)	4 (3.6)	13 (11.6)	11 (100)
Secondarily generalized	10 (28.6)	5 (14.3)	6 (1 1)	4 (11.4)	1 (2.9)	9 (25 7)	35 (100)
Petit mal	10 (91.0)		1 (9.0)				11 (100)
Grand mal	58 (44.3)	1" (13.0)	6 (4.5)	14 (10.7)	6 (4.5)	30 (22.9)	131 (100)
Infantile spasms		1 (9 1)		? (18.2)		8 (72.7)	11 (100)
Akinetic-myoclonic		2 (18.2)		3 ("7.3)	1 (9.1)	5 (45 4)	11 (100)
Unclassified	6 (50.0)	2 (16.7)		1 (8.3)		3 (25.0)	12 (100)
Average per patient	(42.3)	(13.1)	(6.0)	(10.8)	(3.7)	(19.1)	

Different types of epilepsy The intelligence level in different types of epilepsy is pre sented in *Table* 58 Normal intelligence is significantly often found in patients with PM, partial cortical and psychomotor seizures, while profound mental retardation is in highly significant correlation with infantile spasms and akinetic-myoclonic seizures on the Chi Square test.

Prognosis for schooling

Table 59 shows the distribution of the patients according to the degree of education adjusted to the classification of the Central Statistical Office of Finland. Forty five patients (18.4 per cent) had not been considered educable and no scholastic or even ADL education given. One eigth (12.6 per cent) were educable

Table 59. Distribution f the patients by degree of education and in relation to age

Age	N of patients (& percentages) on those with no education	Special education	Primary school	Middle school	High school, Universit	(Percentages of those educated)	No. of patients of the total sample (& percentages)
8	3 (4…9)	2	2			(57.1)	7 (2.9)
9	3 (20.0)	4	8			(80.0)	15 (6.1)
10	9 (50.0)	1	8			(50 0)	18 (7.3)
11	3 (16.7)	5	9	1		(83.3)	18 (7.3)
1…	4 (18 9)	3	9	3		(81.1)	19 (7.8)
13	3 (17 7)	1	9	4		(82.3)	17 (0.9)
14	3 (18.8)	3	6	4		(81.2)	16 (6.5)
15	3 (27.3)	4	2	2		(72.7)	11 (4.5)
16	2 (10.0)	2	9	7		(90.0)	20 (8 2)
17	3 (18.8)	1	11	1		(81.2)	16 (6.5)
18		1	7	1	7	(100.0)	16 (6 5)
19	1 (14.3)		2		4	(85.7)	7 (2.9)
20	1 (14.3)	1	1	1	3	(85 7)	7 (…9)
21	3 ("1.4)	1	4	1	5	(78.6)	14 (5 7)
22	3 (15.0)	2	8	1	6	(85.0)	20 (8.2)
23			2	2	4	(100.0)	8 (3.3)
24	1 (1…5)		3	1	3	(87.5)	8 (3.3)
25			5			(100 0)	5 (2.0)
26			2		1	(100.0)	3 (1…)
Total	45 (18.4)	31 (12.6)	107 (43.7)	29 (11.8)	33 (13.5)		*15 (100)

but not able to start the Finnish compulsory school system which on the other hand, had been completed or was being attended by 69 per cent of the patients. Three patients had started high school and another seven completed it. No more than four patients or 4.7 per cent of those 18 years or over had started university studies and one of them had been graduated at the time of follow up examination.

Table 60. School education of patients in comparison to that of control population

School education	Present series	Control population
	No. of patients (& percentage)	No. of patients (& percentage)
Completed middle school	6 (4.3)	31 353 (8.5)
Passed high school examination	7 (5.0)	21 491 (5.8)

Two control populations were available for comparison. *Table* 60 shows respectively the percentages of the present series and the total population of V-SRPA in relation to educational attainment. The frequency of patients of the present sample who had passed through either middle school or high school was approx. one half of that of the control population.

The degree of education was compared to the population 14—20 years in CTP. Middle school was completed in this age group by 3.3 per cent of patients and 14.3 per cent of controls. The difference is statistically significant. High school examination was passed by 4.6 per cent of patients and 11.4 per cent of controls. This difference is also statistically significant. Of the patients, 1.5 per cent and 1.2 per cent of controls (20 years or more) had passed their university finals.

Intercorrelation (*Table* 61) showed that the degree of education is highly significantly ($p < 0.001$) correlated to an increase in age on the follow-up examination, significantly ($p < 0.01$) correlated to tall stature and heavy weight, and slightly significantly

Table 61. Intercorrelation of variables with school education (n = 135)

Variables	r	p
Age on follow up examination	.297	0.001
Height on follow up examination	.276	0.01
Age at onset of recurrent seizures	.273	0.01
Weight on follow up examination	.256	0.01
School improvement	.211	0.05
Fine motor-adaptive development	.198	0.05
Language development	.198	0.05
Occurrence of status epilepticus	−.181	0.05
Organic aetiology of seizures	−.179	0.05
Duration of follow up period	.145	0.1

($0.01 < p \leq 0.05$) correlated to good school achievement and good fine motor-adaptive and language development. Some statistical dependence was also found between an unfavourable outcome and the occurrence of epileptic statuses and symptomatic aetiology of seizures.

Neither degree of education nor school achievement was in correlation to the occupation of the guardian.

Special education proved to be highly significantly ($p < 0.001$) necessary in cases with

Table 62. Need for special education intercorrelated with different variables (n = 100)

Variables	r	p
Intelligence level	.709	0.001
Full scale intelligence quota	.644	0.001
Head circumference on follow up examination	.607	0.001
Height on follow up examination	.520	0.001
Fine motor-adaptive development	.431	0.001
Personal-social development	.4 [illegible]	0.001
Weight on follow up examination	.360	0.001
Language development	.333	0.001
Short-term results of treatment	.323	0.01
Occurrence of status epilepticus	.301	0.01
Febrile convulsions in close relatives	.285	0.01
Degree of disturbance of consciousness during seizures	.254	0.05
Occurrence of seizures during the latest 12 months	.235	0.05
Age at onset of recurrent seizures	.214	0.05
Duration of phenemal treatment	.187	0.1

a low mental level, small height weight and head circumference on the follow up examination, bad development in fine motor-adaptive personal social and language skills (*Table* 62) A similar need could be shown to exist when there were unsuccessful short term results of treatment, epileptic statuses, or febrile convulsions in close relatives. There was a slight correlation between seizures with complete loss of consciousness, the occurrence of seizures during the latest 12 months and age at the onset of recurrent seizures.

Normal gross motor fine motor mental and language skills highly significantly ($p < 0.005$) correlated with a more advanced school education while the occurrence of psychotic symptoms or hyperkinetic syndrome correlated as strongly with a failure to attend school. The correlation was slightly significant in patients with psychoneurotic symptoms.

School improvement School improvement has been expressed in a mean figure of the marks given in usual reports below university grade (*Table* 63) Four means rejected" 5 to 10 approved

Tabl 63. School improvement (Mean f the marks in school report)

Mean of the marks	N of patients	(Percentage)
< 6	14	(9.1)
6 — 7	33	(21.4)
7 — 8	79	(51.4)
8 — 9	27	(17.0)
9 — 10	1	(0.6)
Total	154	(100)

Intercorrelation showed that in cases where the seizure illness had been severe enough to influence the choice of school type or occupation, even school improvement is unsatisfactory (*Table* 64) The correlation is highly significant, as it is in cases not adequately treated. Correlation to good school improve-

Table 64. Intercorrelation f variables with school improvement

Variables	r	p
Influence on choosing an occupation	—.358	0.001
Adequacy of medical therapy	—.291	0.001
Need for special education	—.500	0.01
Personal-social development	—.267	0.01
Development of personal independence	—.263	0.01
Irregular occip tal rhythmic activity in mean follow-up EEGs	.261	0.01
Language development	—.256	0.01
Number of hospitalizations	—.256	0.01
Fine motor adaptive development	—.233	0.01
Organic aetiology of seizures	—.230	0.01
Occurrence f mental retardation in relatives	—.211	0.01
Capacity for work of those occupied	—.295	0.05
Occupation of a patient	—.277	0.05
Abil ty f r interpersonal contacts	.223	0.05
School education	.211	0.05
Duration f medical therapy	—.209	0.05
Aetiological significance f examination and investigations	—.208	0.05
Number f children in patient family	— 184	0.05
Frequency maximum of seizures	—.183	0.05

ment is significant in cases with normal personal-social and fine motor-adaptive development. A need for special education, irregular occipital rhythmic activity in the follow-up EEGs, probability of an organic aetiology and mental retardation in close relatives, are related to a less favourable improvement.

Analysis with Student s test revealed a highly significant correlation to the intelligence quota and to age at onset of seizures. Patients with a low IQ level and early onset do not improve satisfactorily in school.

Analysis of variance was then performed (*Table* 65) Good school improvement and normal psychomotor development are in significant correlation. The opposite, bad improvement, is as clearly correlated with neurotic and psychotic symptoms and hyperkinetic syndrome and slightly with psychoneurotic symptoms. The occurrence ...

Table 65. Correlation of variables to school improvement on analysis of variance

Variables	(d fr)	F	p
Gross motor state	(1 [illegible]00)	3[illegible].00	0.01
Fine motor state	(1 8[illegible])	14 69	0.01
Mental state	(1 80)	01.17	0.01
Language state	(2, 88)	20.20	0.01
Neurotic symptom	(5 101)	3.013	0 01
Psychotic symptoms	(4 100)	4 0[illegible]	0.01
Hyperkinetic syndrome	(2, 101)	1[illegible]	0 01
Occurrence of occasional seizures	(2, 10[illegible])	4.93[illegible]	0 01
Institutionalization	(1 103)	34 02	0.01
Persistent irregular delta activity in initial EEG	(1 103)	0.860	0.01
Psycho-neurotic symptoms	(8, 100)	2.5[illegible]0	0.01
Unclassified epilepsy	(1 103)	2.500	0 0[illegible]
Acute febrile infection as a seizure provoking factor	(1 103)	4.350	0.0[illegible]

significance occasional seizures and recurrent ones with an acute febrile infection as a provoking factor suggest a bad improvement while, on the other hand, patients with unclassified epilepsy do well in school. An unfavourable outcome is to be expected when an initial EEG shows a local persistent amorphous delta activity

On analysis of variance, normal gross motor fine motor mental and language skills significantly correlated with good school improvement Significantly less improvement was shown by patients with neurotic, psychoneurotic or psychotic symptoms or hyperkinetic syndrome as well as by those with earlier occasional fits or persistent local irregular delta activity in EEG Slight singificance may also be ascribed to an acute febrile infection as a seizure provoking factor

Different types of epilepsy Single types of epilepsy do not seem to have any particular effect in those able to attend school A slightly significant correlation can be found only in cases with unclassified seizures on analysis of variance.

Prognosis for employment

Data on the occupation of 101 patients, 16 years or more were available. The main type of activity of these patients is presented in *Table 66* Forty five were employed outside the home 31 were school children or students and five were working family members (household in own family) Thus, 80.2 per cent of the patients aged 16 years or more were occupied.

Table 66. Main type of activity of the patients (16 years or more)

	N of patients	(Percentage)
Employed	45	(44 6)
School children students	31	(30.)
Working family members	5	(5.0)
Unoccupied	[illegible]0	(10.8)
Total	101	(100)

At the time of the follow up examination, 37 of those occupied outside the home were in permanent, and three in temporary employment One was temporarily unemployed and two were doing their compulsory military service. All five patients who were working family members were chronically unemployed, in spite of their good efforts to acquire work (*Table 67*)

Table 67 Employability of the patients

Employability	No. of patients	(Percentage)
Permanently employed	4[illegible]	(82.3)
Temporarily employed	3	(5.9)
Temporarily unemployed	1	(2.0)
Chronically unemployed	*5*	*(9.8)*
Total	51	(100)

Disadvantageous effect of illness with seizures in choosing a school type or an occupation on the patients aged 10 years or more

Table 68. Disadvantageous influence of epilepsy on choosing a school type r occupation

Amount of influence	No of patients	(Percentage)
No influence	64	(35.2)
Slight to moderate influence	28	(15.4)
Marked influence	22	(12.0)
Completely unable to work	68	(37.4)
Total	182	(100)

is demonstrated in *Table* 68 Data given by the patients showed that roughly one third is unaffected, another third slightly to moder ately and the remaining third maximally affected or incapable of school or employment activities. No such data were available for eleven patients. The remaining 52 patients were under the age of 10.

As to socio-economic status, 27 patients were unskilled and 11 skilled workers, six were in clerical occupations and one had his own enterprise.

When the classification of occupation is made according to Rauhala (277) who studied the social stratification of Finnish society in the 1960's in the light of prestige of occupa

Table 69. Occupation of the patients compared t the guardian's occupation and to the normal distribution (Rauhala 1969)

Rauhala class	Patients		Guardians		Normal distribution	
	No of patients (& percentage)					
No occu-pation	41	(41.4)				
1						
2			4	(1.7)	5.563	(0.3)
3			8	(3.5)	29.073	(1.4)
4	2	(2.0)	20	(8.6)	133.636	(6.6)
5	12	(12.1)	62	(26.7)	246.249	(12.1)
6	10	(10.1)	83	(35.8)	571.627	(28.1)
7	15	(15.2)	43	(18.5)	657.096	(32.3)
8	7	(7.1)	9	(3.9)	322.260	(15.9)
9	12	(12.1)	3	(1.3)	67 664	(3.3)
Total	99	(100)	232	(100)	2.033.268	(100)

tions, a noticeable number of the patients (aged 16 or more) are in the lower (6—9) strata (*Table* 69) Forty one had no occupa tion. The number of patients of the present sample is highly significantly bigger in the lowest stratum (number 9) on Student s test as compared to Rauhala s sample for the whole country (278) His figures, however are not matched to age.

Table 70. Main source of livelihood

	No of patients	(Percentage)
Employment	39	(36 8)
Pension	19	(1 .9)
Social relief loan or scholarship	20	(18.9)
Capital or interest		
Income or property of another person	28	(26.4)
Total	106	(100)

The main source of livelihood of the pa tients 16 years or more is presented in *Table* 70 In thirty nine, this was employment, in 19 a pension due to epilepsy 20 were taken care of by the society (17 institutionalized, 2 in compulsory military service and one studying with the aid of a scholarship) and 28 were living at the expence of their rela tives.

Intercorrelation analysis demonstrated that irregular occipital rhythmic activity on the initial EEG number of hospitalizations, age at the onset of seizures, school improvement, age on the follow up examination and oc cupation of the guardian correlated slightly significantly to the patient's occupation (*Table* 71) When the analysis of variance was ap plied, a good occupational outcome was found in cases where all the aspects of psychomotor state were normal. Patients with hyper kinetic syndrome, institutionalization or psy chotic symptoms are expected to remain permanently without an occupation.

Employability seemed to be highly *signifi*cantly correlated with the occurrence of sei

Table 74. Presenting behavioural disturbances

Behaviour	Neurotic	Psycho-neurotic	Psychotic	Hyperkinetic
	No. of patients (& percentage)			
Not known	39 (16.3)	46 (18.9)	22 (9.1)	23 (1_1)
Normal	68 (28.5)	125 (51.4)	194 (80.1)	130 (54.4)
Abnormal	132 (55.2)	72 (29 ̄)	26 (10.8)	80 (33.5)
Total	239 (100)	243 (100)	242 (100)	239 (100)

Tabl 75 Presenting neurotic symptoms

Neurotic symptoms		No. of patients	(Percentage)
Normal		68	(34.0)
Abnormal			
— obesity	15		
— nail-biting	60		
— enuresis/encopresis	51		
— other	6		
	132	132	(66.0)
Total		200	(100)

Table 76. Presenting psycho-neurotic symptoms

Psycho-neurotic symptoms		No. of patients	(Percentage)
Normal		125	(63.5)
Abnormal			
— phobias	21		
— anxiety	15		
— obsessions	2		
— hysteria	3		
— tic	5		
— depression	15		
— other	11		
	72	̄2	(36.5)
Total		197	(100)

copresis or both (51 patients or 38.6 per cent) were the commonest presenting symptoms. Obese patients, i.e two standard deviations or more above the average height-matched weight, were 15 in number Eight (6.1 per cent) were males and seven (6.5 per cent) females. Compared to the results of a study of 32.000 local primary school children which was made in Helsinki by Helve *et al* (135) where 3 5 per cent of males and 3 0 per cent of females were obese (obesity defined as above) the figures of the present series are almost double.

Phobias, anxiety and depressive states were most frequently present in 72 patients with psycho-neurotic symptoms. Twenty six pa tients (10.8 per cent) had psychosis, chiefly of the autism or symbiosis type.

Eighty six patients (85.1 per cent) showed behavioural symptoms, other than those men tioned above, compatible with cerebral dysfunction. Eighty had hyperkinetic syndrome, 32 specific reading and writing difficulties and 19 adjustment disturbances. No data existed on 35 patients in this regard.

Aetiological conclusions as to an organic background of psychopathology could be drawn in 113 cases (*Table* 77) There are no firm criteria with which to prove the existence or non-existence of an organic cause. However the cause was considered to be definitely organic when clinical examination and various investigations together revealed defect symp-

Table 77 Organic background of psychopathology

Organic background	No. of patients	(Percentage)
Nothing organic	3	(2.6)
Possible organic	23	(20.4)
Probably organic	62	(54.9)
Definitely organic	25	(22.1)
Total	113	(100.0)

Table 79 Frequency of presenting behavioural disturbances in patients with different types of epilepsy (Percentages in parentheses)

	Neurotic		Psycho-neurotic		Psychotic		Hyperkinetic	
	Yes	No	Yes	No	Yes	No	Yes	No
Partial cortical	6 (54.5)	5 (45.5)	3 (30.0)	7 (70.0)	1 (9.0)	10 (91.0)	3 (30.0)	7 (70.0)
Psychomotor	63 (66.3)	32 (33.7)	30 (33.3)	60 (66.7)	13 (12.4)	93 (87.6)	27 (32.5)	56 (67.5)
Secondarily generalized	20 (64.5)	11 (35.5)	12 (44.4)	15 (55.0)	7 (20.6)	27 (79.4)	13 (46.4)	15 (53.6)
Petit mal	6 (60.0)	4 (40.0)	3 (27.3)	8 (72.7)		12 (100.0)	2 (18.2)	9 (81.8)
Grand mal	69 (67.0)	35 (33.0)	42 (39.2)	65 (60.8)	14 (11.6)	107 (88.4)	48 (42.5)	65 (57.5)
Infantile spasms	4 (44.4)	5 (55.6)	3 (30.0)	77 (70.0)	3 (30.0)	7 (70.0)	3 (30.0)	7 (70.0)
Akinetic-myoclonic	7 (77.8)	2 (22.2)	5 (50.0)	5 (50.0)	3 (30.0)	7 (70.0)	5 (55.5)	4 (44.5)
Unclassified	6 (54.5)	5 (45.5)	2 (22.2)	7 (77.8)		9 (100.0)	4 (40.0)	6 (60.0)
Average per patient	(66.0)	(34.0)	(36.5)	(63.5)	(11.8)	(88.2)	(38.1)	(61.9)

cation with infantile spasms and akinetic myoclonic seizures (30 per cent) Akinetic-myoclonic epilepsy was also most frequently represented in patients with hyperkinetic syndrome (55.5 per cent)

Prognosis for psycho-social adjustment

Psycho-social adjustment is an interaction between a patient and his environment. The patient's attitude to the environment and *vice versa* must both the considered.

The development of personal independence is one of the most important qualifications needed for adequate enviromental adaptation of an individual. For an epileptic this means that he has to be capable of all the activities that his healthy peers of the same age can do His mental and motor capacity must be satisfactory he must be able to make social contacts, to act without other people's immediate supervision and, later to earn his living independently

In the present series 105 patients (44.0 per cent) were completely independent, while 56 (23.4 per cent) were entirely dependent on others (*Table* 80) Contacts with other people were frequent or moderately frequent in more than half (52.3 per cent) Forty three were incapable of making any contacts (*Table* 81)

Table 80. Personal independence of the patients

Dependence	N of patients	(Percentage)
Completely independent	105	(44.0)
Slightly to moderately dependent	34	(14.2)
Greatly dependent	44	(18.4)
Completely dependent	56	(23.4)
Total	239	(100)

Table 81. Contacts of the patients with other people outside the family

Contacts	N of patients	(Percentage)
No contacts	43	(27.7)
Infrequent contacts	31	(20.0)
Moderately frequent contacts	62	(40.0)
Frequent contacts	19	(12.3)
Total	155	(100)

Statistical analysis was performed to find the variables that are in significant correlation to the development of personal independence. Intercorrelation of the data revealed a number of highly significant and significant correlations (*Table* 82) Normal psychomotor development and physical growth and non-existence of a symptomatic aetiology of seizures were all highly significantly correlated with a nor

Table 87 Development of personal independence in relation to different types of epilepsy

Type of epilepsy	Completely independent	Slightly to moderately dependent	Greatly dependent	Completely dependent	Total
	No of patients (& percentage)				
Partial cortical	7 (63.6)	2 (18.2)	? (18.2)		11 (100)
Psychomotor	48 (43.3)	21 (18.9)	24 (21.6)	18 (16.2)	111 (100)
Secondarily generalised	13 (37.2)	7 (20.0)	3 (8.6)	12 (34.2)	35 (100)
Petit mal	9 (75.0)	1 (8.3)	2 (16.7)		12 (100)
Grand mal	53 (41.3)	13 (10.1)	28 (21.9)	34 (26.6)	128 (100)
Infantile spasms			? (18..)	9 (81.8)	11 (100)
Akinetic-myoclonic	2 (18..)	1 (9.1)	2 (18.2)	6 (54.5)	11 (100)
Unclassified	5 (41.6)	2 (16.7)	2 (16.7)	3 (25.0)	12 (100)
Average per patient	(44.0)	(14.2)	(18.4)	(23.4)	(100)

Need for institutionalization

Seventy three (29.9 per cent) of the present series had been institutionalized at least once. The institutions in question are for mentally retarded. Indications for admission of epileptics to these institutions were low mental capacity or severe behavioural difficulties. Only few were admitted due to seizures and very few (2 cases) were taken into a special hospital for epileptics. On follow up examination, 49 patients, or ?0 per cent, were seen in institutions. Of them, 21.9 per cent had an unknown aetiology while 9 6 per cent were hereditary 52 per cent organic and 16.5 per cent had both organic and hereditary background. Age at the onset of epilepsy was under one year in 43 8 per cent, 1—2 years in 30.2 per cent and 3—14 years in the rest. The frequency maximum of seizures was in 60.3 per cent several fits a week and in 97.3 per cent more than one a year

Final remission from seizures in institutionalized patients is presented in *Table* 88. Almost two thirds (65.8 per cent) had never had any remission. Freedom from seizures for five years or more had been attained by 17.1 per cent of the patients.

By the use of Student s test, a highly significant correlation was found between institutionalization and, on the other hand, early onset of seizures, long duration of phenemal

Table 88. Institutionalization in relation to final recovery from seizures

Recovery (in yrs)	Institutionalized N of patients (& percentage)	Non institutionalized No of patients (& percentage)
Never	46 (65.8)	60 (35.5)
< 1	5 (7.1)	3 (1.8)
1—2	2 (2.9)	6 (3.6)
?—3		11 (6.5)
3—5	5 (7.1)	18 (10.7)
5—7	7 (10 0)	10 (5.9)
≥ 7	5 (7.1)	61 (36.0)
Total	0 (100)	169 (100)

therapy and a determined low intelligence quota. Short stature on both initial and follow up examinations and low weight on the latter as well as poor school achievement and older age, proved to be typical features in institutionalized patients, as shown by the analysis of variance. Irregular occipital rhythmic activity was not infrequently found in them, too. Older children in birth order seem to have a slightly significantly increased risk for institutionalization.

The Chi Square test demonstrated several variables which are *highly significantly* correlated with institutional care. These are non-existence of final seizure freedom or freedom during the latest 12 month, poor short-term and long-term results of therapy seizures

average standard for the whole country A sewage drain is highly significantly water closet significantly and the rest (excepting water conduit) slightly significantly commoner

Table 85 demonstrates the tenure status of conventional dwellings compared to that of the control population which in this instance consisted of the population of \-SRPA The tenure of an own house or flat is approximately as common in the present as in the control series. Lodgers are possibly less common in the present sample

The attitude of the environment to the patients was known in 107 cases out of 10? who were non institutionalized (*Table* 8) The attitude in forty one (38 3 per cent) was positive while in 20 (18.8 per cent) it was more or less negative Intercorrelation analysis revealed that the environmental attitude was significantly influenced by an occurrence of seizures during the latest 12 months, long term results of treatment and final remission from seizures.

Tabl 8 Ten re t tu t the convent m l d l l ~ f p tent family compared t that t c tnl j p l t n (l rc t ges n j rentheses)

Ten re sta	Present series		Control population	
N t known	1	(10.)	1 11	(1 0)
Owner f ho se	03	(4 4)	6 476	(40 0)
O ner f flat	25	(1_8)	28.2"	(?0 1)
Official residence	1	(8.)	11 3.0	(8 0)
Lodger	40	(20 4)	36 7"	(? 0)

Table 86. Attitude of the env ronment to the patients

Attitude of the environment	No of patients	(Percentage)
Positi	41	(38.3)
Alternating pos t v and negati e	2?	(2_ 4)
Indifferent	2_	(?0.6)
Somewhat negative	10	(9 4)
Definitely negative	10	(9 4)
T tal	10?	(100)

The occurrence of different EEG abnormalities matches a bad adaptation Such abnormalities are irritative paroxysms (in particular hypsarrhythmia below $2\frac{1}{2}$ Hz SpW or poly SpW) irregular occipital rhythmic activity and a high degree of abnormality (in the scale normal — severely abnormal) in both initial and mean follow up EEGs.

Good results from short term and long term medical and especially phenemal therapy highly significantly correlated to a good outcome

A low intelligence level whether judged or determined and a decreasing IQ correspond to a bad outcome as do a need for special education and poor school improvement

A highly significant correlation understandably exist between independence and, on the other hand, good working ability employment, high socio-economic status and a high place in social grouping The owning of a driving licence and completing compulsory military service are further correlated with a good outcome

Variables that are highly significantly correlated to positive enviromental attitude are non-occurrence of the seizures during the latest 12 months and good long term treatment results The attitude of the environment is found to be significantly negative when there is a short remission from seizures in the patient or febrile convulsions in close relatives.

The relationship of different types of epilepsy to the development of personal independence is very variable (*Table* 87) While 75 per cent of cases with PM seizures and 63 6 per cent of those with partial cortical seizures are completely independent, only 18._ per cent of patients with akinetic-myoclonic and none of those with infantile spasms belong to the same group. In the entirely dependent group the figures are vice versa the most invalids were found in epileptics with infantile spasms, akinetic myoclonic or secondarily generalized seizures.

Table 91. Intelligence level in relation to final recovery from seizures

Recovery (in yrs)	Intelligence level, I Q						
	≥ 84	83—68	67—52	51—36	35—20	< 20	Total
	No of patients (& percentage)						
Never	29 (25.4)	17 (53.2)	10 (77.0)	14 (60.8)	4 (44.4)	30 (68.2)	104 (44.0)
<1	2 (1.8)	1 (3.1)			3 (33.3)	2 (4.5)	8 (3.4)
1—2	4 (3.5)	1 (3.1)	1 (7)			3 (6.8)	9 (3.8)
2—3	6 (5.3)	2 (6.3)	1 (7.7)	2 (8.)			11 (4.6)
3—5	13 (11.4)	4 (12.5)		2 (8.7)		4 (9.1)	23 (9.7)
5—7	10 (8.8)	1 (3.1)	1 (7.7)	2 (8.7)		2 (4.5)	16 (7.1)
≥ 7	50 (43.9)	6 (18.7)		3 (13.0)	2 (22.2)	3 (6.8)	64 (27.4)
Total	114 (100)	32 (100)	13 (100)	23 (100)	9 (100)	44 (100)	235 (100)

Table 92. Mean school improvement in relation to final recovery from seizures

Recovery (in yrs)	Improvement (Scale 5—10)					
	5	6	7	8	9	Total
	No of patients (& percentage)					
Never	7 (53.8)	13 (39.4)	25 (31.6)	8 (29.6)	1 (100.0)	54 (35.5)
<1	1 (7.7)	1 (3.0)	1 (1.3)			3 (2.0)
1—2	2 (15.4)	3 (9.1)	1 (1.3)			6 (4.0)
2—3	1 ([illegible])	1 (3.0)	3 (3.8)	5 (18.5)		10 (6.6)
3—5		2 (6.1)	13 (16.5)	2 (7.4)		17 (11.4)
5—7	1 (7.7)	2 (6.1)	5 (6.3)	3 (11.1)		11 (7.2)
≥7	1 (7.7)	11 (33.3)	31 (39.2)	8 (33.3)		51 (33.3)
Total	13 (100)	33 (100)	79 (100)	26 (100)	1 (100)	15[illegible] (100)

Table 93. Employability in relation to final reco ery from seizures

Recovery (in yrs)	Employment	Pension	Relief	Income of another person	Total
	No. of patients (& percentage)				
Never	12 (30.8)	14 (73.6)	10 (56.0)	13 (46.4)	40 (40.0)
<1	1 (2.6)	1 (5.3)			2 (2.0)
1—2	2 (5.1)	1 (5.3)		1 (3.6)	4 (4.0)
2—3	3 (7.7)			1 (3.6)	4 (4.0)
3—5	6 (15.3)	2 (10.5)		2 (7.1)	10 (10.0)
5—7	3 (7.7)	1 (5.3)	4 (22.5)	1 (3.6)	5 (5.0)
≥7	12 (30.8)		4 (22.5)	10 (35.7)	26 (26.0)
Total	39 (100)	19 (100)	18 (100)	28 (100)	100 (100)

test. School education was statistically even better in patients than in controls.

In *Table* 93, where employability is cross-tabulated with the final recovery from seizures, it may be seen that as many patients are employed of those with no final remission as of those with remission of more than seven years. Thus, no difference can be demonstrated in regard to the presence or absence of seizures.

Different *behavioural disturbances* (*Table* 94) were not found to be correlated with final recovery from seizures on the Chi Square test.

A highly significant ($p < 0.0005$) correlation was found between *institutionalization* of the patients and persistent seizures (*Table* 88).

Mortality is quite often caused or contributed to by an epileptic attack, for which reason it is no wonder that patients with no remission from fits are more prone to early death than others (*Table* 9[illegible]).

Table 94. Behavioural disturbances in relation to final recovery from seizures

Recovery (in yrs)	Neurotic	[illegible]	[illegible]	Hyperkinetic
	No. of patients (& percentage)			
Never	5[illegible] (40.0)	31 (4[illegible].8)	16 (61.6)	38 (48.[illegible])
<1	6 (4.6)	4 (5.6)	[illegible] ([illegible])	[illegible] (6.4)
1—[illegible]	3 (2.3)	6 (8.[illegible])		[illegible] ([illegible])
2—3	[illegible] (5.1)	[illegible] (2.8)		1 (1.1)
3—5	13 (10.0)	6 (8.[illegible])	[illegible] ( )	9 (11.[illegible])
5—	13 (10.0)	4 (5.6)	2 ([illegible]7)	8 (10.2)
≥	36 ([illegible])	1 ([illegible]1.2)	4 (1[illegible].3)	1[illegible] (10.2)
Total	130 (100)	[illegible]1 (100)	[illegible] (100)	[illegible]8 (100)

Table 95. Mortality in relation to final recovery from seizures

Recovery (in yrs)	Dead	Alive
	No. of patients (& percentage)	No. of patients (& percentage)
Never	16 (89.0)	90 (40.5)
<1		8 (3.6)
1—		9 (4.1)
—3	1 (5.5)	10 (4.5)
3—5	1 (5.5)	— (0.0)
5—7		1 ( )
≥7		66 (29)
Total	18 (100)	— (100)

F. MORTALITY

Eighteen (7.4 per cent) of the patients died during the follow up period. These cases are presented in *Table* 96. There were nine males and nine females. The mean age at the onset of epilepsy was 25 months. In 12 cases, there was a symptomatic aetiology and in another case it was both hereditary and symptomatic. Three patients had an unknown and two cases a hereditary aetiology.

Psychomotor development was abnormal in all but four cases. No less than 16 were abnormal on the neurological follow up examination. GM occurred in eleven cases, psychomotor seizures in seven and partial seizures secondarily generalized in three cases. Initial EEG was normal in one of the 14 cases investigated and markedly abnormal in ten. All the mean follow up EEGs were abnormal or markedly abnormal.

Eleven were institutionalized at death. Cause of death was drowning in five patients and pneumonia or other respiratory tract infection in six cases who were all cerebrally palsied, profoundly mentally retarded patients. There was sudden death in two patients and another cause in two more cases.

In altogether six cases an epileptic attack was the cause of or contributory to death, and in two more cases, it was suspected. In three cases, the mechanism of death was drowning. The cause of death of seven patients was confirmed at autopsy.

On the analysis of variance, a significant correlation of a risk for death to early age at the onset of seizures and low IQ was found. Duration of medical therapy was in sligtly significant correlation, too.

Table 96. Cases who died during follow-up period (M = male, F = female)

	Sex	Age at onset of seizures	Aetiology	Psycho-motor development	Neuro-logical state	Epilepsy diagnosis	Institution-alization	Age at death	Cause of death	Contribution of seizure to death
1. L.G.H.	M	0:9	unknown	abnormal	normal	psychomotor GM	yes	19 11	drowning (suicide)	no
2. M.N.H.	M	7	symptomatic	normal	abnormal	GM	yes	16 ?	pneumonia	no
3. J.E.H.	M	0 4	hereditary	abnormal	abnormal	GM	yes	3:7	upper resp. tract inf.	no
4. P H.	M	5·0	symptomatic	normal	abnormal	psychomotor second. generalized	no	23·0	drowning	yes
5. M.L.H.	F	0:5	symptomatic	abnormal	abnormal	GM	yes	7.10	bronchitis	no
6. A.L.K.	F	8 0	symptomatic	normal	abnormal	psychomotor	no	3 10	sudden death	yes?
7. J.H.K.	M	0	symptomatic?	abnormal	abnormal	infantile spasms, psychomotor	yes	0:11	pneumonia	no
8. M.O.L.	M	0·6	hereditary & symptomatic	abnormal	abnormal	psychomotor GM	yes	17 4	drowning	yes
9. R.T.L.	M	0:9	unknown	abnormal	abnormal	GM	no	11:5	drowning	no
10. R.K.L.	F	0.8	symptomatic?	abnormal	abnormal	akinetic-myoclonic, GM	no	5 7	sudden death	yes?
11. T.V.M.	M	0 4	symptomatic	abnormal	abnormal	unclassified	no	7	epil. seizure	yes
12. A.K.N.	F	0 4	hereditary	abnormal	abnormal	GM	no	2 7	status epilept.	yes
13. M.V.P.	F	2:2	symptomatic?	abnormal	abnormal	second. generalized	yes	7 0	drowning	yes
14. M.M.S.	F	·0	symptomatic	abnormal	abnormal	psychomotor sec. gener	yes	15 3	pneumonia	no
15. M.I.S.	F	0.1	symptomatic	abnormal	abnormal	GM	yes	8:2	epil. seizure	yes
16. S.S.	F	4 6	symptomatic?	normal	normal	GM	no	11:0	heart insuff. bronch. asthma	no
17. M.I.S.	F	1 0	symptomatic	abnormal	abnormal	psychomotor GM	yes	13:1	pneumonia	no
18. J.K.T.	M	?·6	unknown	abnormal	abnormal	GM	yes	10.5	peritonitis	no

VI DISCUSSION

Prevalence and incidence The prevalence rate of 3.2 per 1000 (at least three seizures with the minimum interval of a week) or 4.0 per 1000 (at least one defined epileptic seizure) is comparable to figures reported from other Scandinavian or European countries. The rate of 2.4[illegible] per 1000 calculated by Halkaralnen *et al* (12[illegible]) is far too low It is obvious that certificates for obtaining anticonvulsant drugs free of charge are not written for patients in the paediatric age group as readily as for adult epileptics. One would first rather wait and see whether epilepsy will actually develop or not It is estimated that half of them are receiving drugs free of charge Calculated thus, the figure of 3.28 per 1000 is obtained, equalling the rate of 3.2 per 1000 of the present study The prevalence rate is higher in males, as in Kurland's study

Comparable data for the age 0—9 years show that the rate of 3.3 per 1000 corresponds rather well to 3.3 of Brevis *et al* (29) 3.6 of Brorson (32) 4.[illegible] of Gudmundsson (116) and 5.8 per 1000 of Kurland (198) In Brorson's study even cases with one epileptic seizure before successful drug therapy were included (33)

If the figures obtained in the present study were applied to the total population of the zure) is comparable to figures reported from country then there would be 2000 males and 1500 females aged 0—1[illegible] with an epilepsy

The average annual incidence of epilepsy is 7.8 per cent of the average prevalence The rate in the first year of life — 0.9[illegible] per 1000 — in the present study compares well to the rate of 1.0 per 1000 cases with two or more seizures without fever in Mäkinen's study ([illegible]1) Similarly compared as five-year groups to the rates of Brevis *et al* ([illegible]9) and Kurland (1[illegible]) the figures are reasonably well in agreement (*Table* [illegible]7) However the figures of the two latter reports are somewhat higher than those of the present study Kurland's rather high figures in the first year of life and relatively low rates in later years could be understood if the first (occasional) seizure instead of the first of the *recurrent* seizures was regarded as the onset of epilepsy even though no information is given on this in his paper

Table [illegible] Average annual incidence of epilepsy Comparison of the present series to reports in the literature

Age (in yrs)	Average annual incidence per 1000		
	Present series	Brevis et al (1964)	Kurland (19[illegible])
0 — 4	0.4[illegible]	0.[illegible]	1.5[illegible]
5 — 9	0.3[illegible]	0.36	0.2[illegible]
10 — 14	0.2[illegible]	0.41	0.25

If the figures of the present study were applied to the total population of the country then 1[illegible]0 males and 12[illegible] females, or approx. 300 new cases of epilepsy 0—15 years of age would develop each year This means that every 4000th person of this age will annually start to have recurrent seizures.

Demographic and medical data. Eleven (4.5 per cent) of the patients of the present series were premature 22 (9.0 per cent) small for date and 9 (3.7 per cent) postmature. When these frequencies are compared to Rantakallio's (276) figures derived from 12.068 births during one year in northern Finland (4.13 per cent premature, 1.1? per cent small for date and 5.65 per cent postmature) a preponderance of small for dates is found, while the frequency of pre and postmatures is below the average. However the frequency of prematurity is higher in the present series than in Klemetti's (190) series from Helsinki, where the frequency was 3.2 per cent of 3 463 cases.

Neonatal asphyxia was found in 40 patients (16.3 per cent) which is comparable to 13.9 per cent of cases in Bronson's (32) sample. In Iivanainen's (150) sample of 338 cases with mental retardation, there was a "slight asphyxia" in 21.9 per cent and "marked asphyxia" in 9.2 per cent of cases. No more than 4.6 per cent of 7 024 liveborn babies in the Departments of Obstetrics, University of Helsinki (302) had "marked asphyxia"

The present series does not differ essentially from those previously reported as to sex distribution (3, 62, 148) age at onset (3, 31, 32, 163 206) aetiology (91 174, 206) neurological state (32, 148) or different types of epilepsy (16 31 32, 163 194 206)

Male preponderance is clear especially during the first five years. Age at onset is most frequent during the first three years (in 57.0 per cent) but a small rise in incidence is also found at age 5—6 years, corresponding to the top frequency of cryptogenic epilepsy in Livingston's series (1954)

Epileptic children were significantly often the first children in the family However the distribution of children according to birth order does not differ from the average population.

The general impression during clinical examination was that the patients had shorter stature and lower body weight, as compared to the average. However this was not the case concerning height, weight or maximum head circumference on statistical analysis.

Age at menarche differed statistically significantly from controls. Brain damage might be a reason for disturbed hormonal control in these cases though no significant correlation to an organic cause of seizures could be demonstrated.

Neuropsychiatric disorders are commoner in relatives of epileptics than in the average population. Recurrent seizures in 13.5 per cent of relatives is a proportionally high frequency

The frequency of toxaemia of pregnancy (15.1 per cent) is significantly higher than 5.5 per cent of altogether 17 690 pregnancies in Turku 1965—66 and 1968—70 (279)

Gross motor development was retarded on the basis of cerebral palsy in 64 cases, or 26.1 per cent, which is in rather close agreement with Bronson's figure of 22.7 per cent. An intellectual handicap occurred in his study in 42.8 per cent (IQ 89 or less on *e.g* Goodenough's and WISC tests) The corresponding figure in the present study is 57 7 per cent (IQ 85 or less)

Different types of epilepsy The classification of epilepsy varies from report to report and no agreement has been reached as yet. According to most papers, however GM seems to be the commonest type, although more and more cases have been explained to have partial seizures and GM comprehended in the concise sense of Penfield and Jasper (269) with no traceable local signs in EEG In Bronson's (32) study where the International Classification of Epileptic Seizures (93) had been applied, the distribution of different types was very similar to that of the present study (*Table* 98)

In GM, the first EEG may be normal and "not seldom" (22) are local changes found in initial or follow-up EEGs. On the other hand, local findings in EEG occur in approx

VI DISCUSSION

Prevalence and incidence The prevalence rate of 3.2 per 1000 (at least three seizures with the minimum interval of a week) or 4.0 per 1000 (at least one defined epileptic seizure) is comparable to figures reported from other Scandinavian or European countries. The rate of 2.45 per 1000 calculated by Halkaralnen *et al* (12.) is far too low It is obvious that certificates for obtaining anticonvulsant drugs free of charge are not written for patients in the paediatric age group as readily as for adult epileptics. One would first rather wait and see whether epilepsy will actually develop or not. It is estimated that half of them are receiving drugs free of charg Calculated thus, the figure of 3.28 per 1000 is obtained, equalling the rate of 3.. per 1000 of the present study. The prevalence rate is higher in males, as in Kurland's study

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Table 9? Average annual incidence of epilepsy Comparison of the present series to two samples in the literature

Age (in yrs)	Average annual incidence per 1000		
	Present series	Brevis *et al.* (1966)	Kurland ([illegible])
0 — 4	0.4	[illegible]	1.5
5 — 9	0.3	0.36	0.25
10 — 14	0.20	0.41	0.23

If the figures of the present study were applied to the total population of the country then 170 males and 125 females, or approx. 300 new cases of epilepsy 0—15 years of age would develop each year This means that every 4000th person of this age will annually start to have recurrent seizures.

Demographic and medical data. Eleven (4.5 per cent) of the patients of the present series were premature 22 (9.0 per cent) small for date and 9 (3.7 per cent) postmature. When these frequencies are compared to *Rantakallio's* (276) figures derived from 12.068 births during one year in northern Finland (4.13 per cent premature, 1.12 per cent small for date and 5.65 per cent postmature) a preponderance of small for dates is found, while the frequency of pre and postmatures is below the average. However the frequency of prematurity is higher in the present series than in Klemetti's (190) series from Helsinki, where the frequency was 3.2 per cent of 3 463 cases.

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Different types of epilepsy. The classification of epilepsy varies from report to report and no agreement has been reached as yet. According to most papers, however GM seems to be the commonest type, although more and more cases have been explained to have partial seizures and GM comprehended in the concise sense of Penfield and Jasper (269) with no traceable local signs in EEG. In Brorson's (32) study where the International Classification of Epileptic Seizures (93) had been applied, the distribution of different types was very similar to that of the present study (*Table* 93).

In GM, the first EEG may be normal and "not seldom" (22) are local changes found in initial or follow-up EEGs. On the other hand, local findings in EEG

Table 08 Comparison of distribution of different types of epilepsy in the present series to a Swedish sample (Brorson 1970)

Different types	Present series — No. of patients (& percentage)		Swedish series — No. of patients (& percentage)	
Partial cortical	11	(4.5)		
			69	(32.0)
Psychomotor	114	(46.)		
Secondarily generalized	36	(14.7)	30	(1)
Petit mal	12	(4.9)	7	(3.0)
Grand mal	131	(3.5)	94	(48.5)
Infantile spasms	11	(4.5)		
			20	(10.3)
Akinetic-myoclonic	11	(4)		
Unclassified	1	(4.0)	11	(.)

one half of paediatric patients in association with psychomotor seizures (22)

Niedermeyer (255) stressed the unstable character of the central local spikes, which are easily deactivated with diazepam when occurring in school children and are evidently not indicative of an organic lesion.

Matthes (236) divided psychomotor epilepsy into centrencephalic temporal and multifocal types. The centrencephalic type made up 17.8 per cent of his sample (135 patients) Many similarities existed to centrencephalic epilepsies.

Christian (49) stated that sharp potentials of a temporal or temporo-basal origin are typical of but not inevitably proof of a psychomotor epilepsy

As can be seen current opinions and concepts are divided as to the differentiation of even partial and centrencephalic seizures from each other

The frequency of GM status epilepticus — in 22.5 per cent — is remarkably high. Hunter's (149) 1.3 per cent and Lennox's (206) 7.5 per cent are essentially lower The difference may be due to different definitions of status and different age groups.

Final recovery from seizures Final recovery from seizures occurred in 27.4 per cent for more than seven years and in 44.0 per cent for more than three years. The figures obtained are clearly below the optimistic reports of "healing" in 75—85 per cent of cases (82, 17 333) but are approx. twice as good as the figures which are common in the literature as reviewed by Rodin (282) An inverse relationship between the long duration of follow up period and a decreasing number of seizure free patients could be confirmed in the present study (*Table 51*)

Patients whose mental and motor development as well as physical growth are normal and whose EEG is normal, or will be normalized in the course of seizure illness, are prone to become free from seizures. On the other hand, patients with brain damage and *consequently retarded* psychomotor development or physical growth will be expected to have an unfavourable outcome Similarly the severity of clinical manifestations is of significance cases with frequent seizures, epileptic statuses and several types of epilepsy occurring irrespective of the time of day commonly have persistent seizures. Furthermore different investigations indicative of organic brain damage are usually refractory to treatment

No significant differences seem to exist between different types of epilepsy Although PM seizures not infrequently cease prior to or at puberty they are often followed by GM seizures. Admittedly infantile spasm and akinetic-myoclonic seizures are even more frequently combined with other seizures than are the other types, particularly GM attacks.

The prognosis for seizures is highly significantly better when the initial seizure type remains isolated than in cases where epileptogenesis is manifested as several types of fits.

The adequacy of medical therapy in comparison to final recovery from seizures did not seem to have significance, however surprising this may seem. The result was even better in cases where a suspicion of inadequate therapy had arisen. This may partly depend on neglecting to take one's medicines, which is a complicated medico-social problem (70 88, 133) The only slight significance seems to

exist between adequate therapy and, on the other hand, a good short-term result of treatment and disappearance of bilateral SpW discharges in EEG

Intelligence More than half the patients (52.7 per cent) were found to be mentally retarded (IQ 85 or less) in the initial examination. At least 60 per cent had further mental deterioration in the course of the disease. In the group of unchanged, a considerable number were not testable due to profound retardation, but apparently the process was progressing in them, too. On the follow up examination an abnormal mental level was found in 54 6 per cent. The conclusion may be drawn that almost all the patients were already initially mentally retarded and that further deterioration was generally taking place.

Factors influencing intelligence prognosis are grossly the same as in the seizure outlook. Mental inferiority is to be expected in cases with an organic backround of seizures which is manifested by abnormal psychomotor and often physical development, early age at the onset of seizures with occurrence both at night and daytime, frequent epileptic statuses, pathological EEG and refractoriness to medical treatment. A highly significant correlation exists between an organic aetiology and low intelligence level on the intercorrelation test. The same fact is reflected by more frequent intellectual handicaps in apparently symptomatic types of epilepsy such as infantile spasms, akinetic-myoclonic, partial and secondarily generalized seizures.

Schooling School education is essentially worse in the present series compared to the average population of corresponding age Thirty one per cent were not educable or were in need of special education, which is much more than on the average. It is noticeable that seizures are significantly correlated to school education only occurring as epileptic statuses. On the other hand, physical growth and psychomotor development and neurological state are highly significantly correlated

Poor school improvement is closely associated with organic brain damage and subsequently an abnormal neurological state, early onset of seizures and low intelligence In addition, however behavioural disturbances, adequacy of medical therapy and the occurrence of occasional seizures have a statistical significance. Febrile infection is also of slight significance as a seizure provoking factor On the other hand, febrile convulsions are found with significant frequency in patients with a need for special education whose close relatives have or have had febrile convulsions. It appears, then, that occasional seizures and particularly febrile convulsions influence school improvement, which is better with adequate medical therapy Recurrent seizures, however seem to have no noticeable significance.

Employment In the present series four out of five (80.2 per cent) aged 16 or more were employed. This corresponds well to the figures reported earlier (63, 174 222, 272) Whether the patients have an occupation or not depends on the neurological state and absence of behavioural disturbances, not on the presence or absence of seizures. However choosing an occupation seems to be markedly influenced by epilepsy and it is often inferior to that of the average and, together with the occurrence of seizures, significantly affects the employability

Behaviour An organic cause was not infrequently found for behavioural changes. This was also supported by neurological abnormalities occurring highly significantly often in these patients It is noticeable that neurotic and psycho-neurotic disturbances occurred in as many as 9 out of 1_ patients with PM although only three of them had a suggested organic aetiology The frequency is almost as common as in other types of epilepsy

The long duration of medical therapy was significantly correlated with the occurrence of psycho-neurotic symptoms. However one

more apt to consider the duration of seizure illness, rather than the duration of medical therapy as having been the cause of psychopathology

Psycho-social adjustment The adjustment of a patient to his environment can be measured in many ways but none of them is accurate enough to give the whole truth. In the present study one of the most important criteria accepted was the development of the personal independence of a patient i.e. the ability to manage with the activities of daily living mental and social maturity and other mental and physical performances with regard to their age The judgement was made partly by the patient's guardian, usually parents partly by the present author with a critical attitude to information from the case journal results of the clinical examination and guardian's report Forty four per cent were completely independent in relation to their age while 14.2 per cent were slightly to moderately in need of another person's aid. Great dependence was shown by 18.4 per cent of cases, who could only carry out a part of the activities of daily living Finally 23.4 per cent were completely helpless in all respects. However it must be stated that epileptic seizures in themselves seldom caused disability The basic disease brain damage usually emerged as the cause of it.

A *definitely abnormal distribution occurred* concerning compulsory military service marital status, driving licence *etc* As could be expected, only few completed compulsory military service often doing less demanding tasks. Some few were married. Though the patients may have felt ashamed of their seizures, the behavioural changes probably had more influence This was confirmed by significantly good adjustment in cases with a normal psychomotor state and non-existence of symptoms of organic aetiology Some few were allowed to have a driving licence

When the families of the patients are compared to the average control population the social circumstances are as good or better in the patient's families than in controls. Thus, no correlation to lower social strata can be demonstrated in epilepties.

Institutionalization In the present series, a considerable number of the patients, namely 29.9 per cent had been in institutional care one or more times. This figure is much higher than those reported in the literature (137 164 272) In part this is due to the well developed network of central institutions for mentally retarded, and to easier admission into institutions, but the chief indication for admission has been a grave intelligence defect or behavioural disturbance

Organic aetiology is in many ways reflected in institutionalized patients. Symptomatic epilepsy early onset of seizures, low intelligence level prognostically poor types of epilepsy *etc* are typical of these patients and characteristic *of brain damage*

Comparison of different prognoses A comparison of different prognoses to final recovery from seizures shows that these may differ significantly from each other A prognosis for intelligence need for institutional care and the mortality rate are significantly correlated with the non-existence of final recovery while a prognosis for behaviour school improvement and employment are in no correlation to the seizure outcome

Mortality Approximately one per cent of cases died annually during the follow-up period When the mortality rate was 7.3 per cent and the average annual incidence of new cases 7.8 per cent one may expect a slow increase in epilepsy frequency in the paediatric age group Two thirds had an organic cause of death In six or possibly eight (44.4 per cent) out of 18 epilepsy contributed to death Only one (5.6 per cent) however had status epilepticus. Drowning was a mechanism of death in 5 cases. Of the total series, this accounts for 2.0 per cent. In comparison to the frequency of 19.5 per 100 000 in the county of Turku and Pori 1962—1965 (195) the drowning frequency is 100 times greater in the present series. One of the drowned patients was the only suicide case of the present series.

VII SUMMARY

The objects of the present study were to investigate the prevalence and incidence rates of epilepsy and to elucidate the prognosis from medical and various social points of view in the paediatric population in South western Finland.

The study was based on the patients collected in available ways and consisted of 348 children 0—15 years of age, with permanent residence in the Turku University Central Hospital region (population 109019 0—15 years of age 31 12. 1970) and with a presence of defined recurrent epileptic seizures in 1961—64. Great attention was paid to the definition of epilepsy and exclusion of occasional attacks, nonepileptic fits and of seizures associated with progressive intracranial processes.

A number of the patients, i.e. 245 hospitalized for epilepsy in 1961—64, were taken for closer examination, investigations and statistical analysis. After the mean follow-up of 129 months, the patients were examined and investigated and previous available data collected by use of a special form. The data material collected was then statistically analysed.

A number of control series were employed, mostly derived from the census of 31 12. 1970 and from the "Healthy child project carried out in Finland since the 1960 s. The controls were used mainly for statistical comparisons of different social prognostic aspects.

Prevalence and incidence of epilepsy Results from the analysis showed that the average prevalence for epilepsy in the population aged 0—15 years is 3.2 per 1000 (males 3 6 and females 2.8 per 1000)

If cases with one defined epileptic seizure are also included, as has been the case in some previous papers, then the rate of 4.0 is obtained. These figures compare well with previous reports from other countries.

The average annual incidence of epilepsy in the same population is 0.25 per 1000 Males are here, as in prevalence rates, more frequently represented. The incidence rate is in agreement with data in the previous literature.

Present sample The present sample did not substantially differ from previous ones in various aspects, such as sex distribution (54.7 per cent males) age at onset (60.6 per cent at the age of 0—3 years) suggested aetiology (in 53.1 per cent either organic or both organic and hereditary) neurological state (in 36 per cent abnormal gross motor state, in 52.7 per cent intelligence level 85 or less and in 39 6 per cent 51 or less) or different types of epilepsy (in 53.5 per cent grand mal, in 46.5 psychomotor and in 4.9 per cent genuine petit mal fits)

Grand mal was the most frequent type of epilepsy (in 63.5 per cent of cases) but psychomotor seizures were almost as common (40.5 per cent) Secondarily generalized partial seizures occurred in 14.7 per cent of partial seizures occurred in 14.7 per cent of patients Each of other types was found in approx. 5 per cent. One hundred and sixty

eight (68.5 per cent) had a single seizure type. The rest had different combinations, most commonly psychomotor fits combined with grand mal or secondarily generalized seizures.

Final remission from seizures for 7 years or more was present in 27.4 per cent, for 5 years or more in 34.5 and for 3 years or more in 44.6 per cent. No final recovery occurred in 44 per cent of cases.

A good seizure prognosis was statistically significantly found in cases with good short term results of treatment, normal psychomotor development and neurological state and normal EEG.

A bad prognosis for epilepsy may be expected in cases with long duration of seizure illness, high frequency maximum of seizures, occurrence of attacks both at night and day time, combined seizure types, cluster occurrence, frequent epileptic statuses, low intelligence level, completely disturbed consciousness in seizures, organic aetiology of fits, occurrence of mental disorders in close relatives, small head circumference and "organic" features in different investigations. No statistically significant correlation could be demonstrated between age at the onset of seizures and final remission from them. Similarly no seizure type proved to be significantly better than the others as to final recovery, greatly due to subsequent combinations of the other types.

Intelligence level was normal (IQ 86 or more) in 47.3 per cent of cases, deficient in 13.1 per cent, mildly to moderately abnormal in 16.8 per cent and gravely to profoundly abnormal in 22.8 per cent. During the follow up the intellectual capacity was decreasing in 60.6 per cent, unchanged (patients mostly profoundly retarded and untestable) in 36.6 per cent. An increasing level was demonstrated in 2.8 per cent.

Factors influencing the intelligence prognosis were mainly the same as in the seizure prognosis. Poor physical growth (height, weight, head circumference) and early onset of seizures highly significantly correlated to a low mental level. Not unexpectedly an initially high intelligence level was best preserved in petit mal fits. Even patients with psychomotor seizures did well. The worst outlook is associated with infantile spasms, akinetic myoclonic and secondarily generalized seizures.

School education is significantly worse in epileptics. Education was completely impossible in 31 per cent. However significantly more of the patients had compeleted middle and high school than of the age-matched control population of similar age. Retarded physical and mental development are highly intercorrelated. School achievement is significantly influenced by the occurrence of organic brain damage, abnormal neurological state, early onset of seizures, low intelligence and behavioural disturbances. A statistical significance was even indicated by febrile infections as a seizure provoking factor and febrile convulsions in close relatives.

Employment. Four out of five (80.2 per cent) aged 16 years or more were employed. The prognosis for occupation depends on the neurological state and behavioural pattern, while choosing an occupation is markedly influenced by seizure illness. Employability in turn depends mainly on the occurrence of seizures and capacity for work.

Employment is most often the main source of livelihood in patients with partial cortical and petit mal seizures. Complete economic dependence on another person was found in one fourth to one third of cases in all seizure types.

Behavioural disturbances. Neurotic symptoms occurred in 50.2 per cent, psychoneurotic in 20.7 and psychotic in 10.8 per cent. Hyperkinetic syndrome was revealed in 33.5 per cent of cases. Nail biting and enuresis or encopresis or both were the commonest neurotic features. Different phobias, anxiety and depressive con-

ditions prevailed in psycho-neurotic cases. Autism and symbiosis were the most usual psychotic manifestations. A probable or defined organic background was felt to have been present in 77 per cent of cases with different psychopathology.

Retarded physical growth correlated significantly to the occurrence of behavioural difficulties. Similarly early age at menarche showed a significant corelation, as did the duration of medical treatment.

Neurotic symptoms occurred mostly in cases with akinetic-myoclonic (77.8 per cent) psychomotor (66.3 per cent) secondarily generalized (64.5 per cent) and petit mal (60.0 per cent) seizures. Psycho-neurotic symptomatology appeared to be most usual in cases with akinetic-myoclonic (50.0 per cent) secondarily generalized (44.4 per cent) and grand mal (39.2 per cent) fits. Autism was found in infantile spasms and akinetic myoclonic seizures more than in other types. Finally hyperkinetic syndrome was mostly associated with akinetic-myoclonic (55.5 per cent) secondarily generalized (46.4 per cent) and grand mal (42.5 per cent) seizures.

Psycho-social adjustment was calculated by the use of various criteria, e.g. capacity for interpersonal contacts, compulsory military service, driving licence, marital status *etc.* All these criteria showed that under representation prevails in the epileptic population as compared to the control populations.

One essential aspect is personal independence as to the activities of daily living, capacity for interpersonal contacts, ability to orientate in relation to time, place and oneself, managing without the aid of others, earning one's living and taking care of one's relatives. By the use of intercorrelation, several group variables correlated to personal independence were obtained. These are normal development and neurological state, normal physical growth, non-organic cause of seizures, benign seizure manifestation (late onset, low frequency maximum, no statuses, occurrence of temporary and final remission from seizures) normal EEG a good result from treatment and normal intelligence.

Social background and particularly family environment was elucidated by using different variables. Classification according to the prestige of occupations showed that the guardians of the patients were highly significantly more in the upper social strata than in the average population. On the other hand, more guardians were divorced or had an illegitimate child than in the control population. The conventional dwellings of families of the epileptics were as good or better than those of the control populations concerning number of rooms, rooms per capita, facilities and tenure status of the dwelling.

The general attitude of the environment was definitely negative in 9.4 per cent of cases and somewhat negative in another 9.4 per cent, while in 81.2 per cent, the attitude was more or less positive.

Institutionalization. As much as 29.9 per cent of cases had been institutionalized one or more times for short term, and 20 per cent for a long term period or permanently. The figure is markedly high in comparison to previous reports. Institutionalization was, however in all but two cases due to serious mental retardation or behavioural disturbances.

Typical of institutionalized patients was commonly (in 68.5 per cent) found a probable or defined organic aetiology of epilepsy and consequently an early onset of seizures, low intelligence level, prognostically poor types of epilepsy such as infantile spasms and akinetic-myoclonic seizures, frequent epileptic statuses, both sleep and waking seizures and generally abnormal EEG.

A comparison of final recovery from seizures to different other prognoses shows that they are far from uniform. Persistent seizures with no remission are accompanied by a low intelligence level, employment, need for insti-

tutional care and shortened life expectancy However behavioural di turbances and prognosis for school achievement are not correlated to the final remission

Mortality was in the present series 7 3 per cent, or one per cent annually As the average annual incidence was 7.8 per cent of prevalence epilepsy may be expected to increase slowly in the paediatric age group

Two third of those who died had an organic cause of seizures. In eight (44 4 per cent) out of 18 cases epilepsy contributed to death. Of them only one had status epilepticus as a cause of d ath. Drowning was a mechanism of death in 5 cases. Percentage-wise this is one hundred times greater than in the average population

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Matti Sillanpää

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APPENDIX I

QUESTIONNAIRE AND EXAMINATION FORM VARIABLES USED

Figures before variables refer to following tests

1 = "missing data" intercorrelation
2 = Student's t-test
3 = Analysis of variance
4 = Chi Square test
5 = Test for equality of two hypothetical frequences

Name of the patient ————————————

DATA CARD I.

Identification

1 Date of birth
1, 2, 3 Length or follow-up
2, 3 Date of follow-up examination
2 4 Sex

Hospitalizations

University hospital
Other central hospital
District hospital
Municipal hospital
3, 4 Institution for mentally retarded
1 No. of hospitalizations
- 0 not recorded
- 1 once
- 2 2—4 times
- 3 5 or more times

Family history

1 Mental retardation
- 0 not recorded
- 1 no
- 2 on paternal side
- 3 on maternal side
- 4 on both paternal and maternal side
- 5 in patient's family
- 0 sex not recorded
- 1 male
- 2 female
- 3 both male and female

————————————

————————————

1 Motor retardation
- 0 not recorded
- 1 no
- 2 on paternal side
- 3 on maternal side
- 4 on both paternal and maternal side
- 5 in patient's family
- 0 sex not recorded
- 1 male
- 2 female
- 3 both male and female

————————————

————————————

1 Psychic disorders
- 0 not recorded
- 1 no
- 2 on paternal side
- 3 on maternal side
- 4 on both paternal and maternal side
- 5 in patient's family
- 0 sex not recorded
- 1 male
- 2 female
- 3 both male and female

————————————

————————————

1 Abortions
- 0 not recorded
- 1 no
- 2 on paternal side
- 3 on maternal side
- 4 on both paternal and maternal side
- 5 in patient's family

1 Congenital malformations
- 0 not recorded

1 no
2 on paternal side
3 on maternal side
4 on both paternal
and maternal side
5 in patient's family
0 sex not recorded
1 male
2 female
3 both male and female

____

____

1 Febrile convulsions
0 not recorded
1 no
2 on paternal side
3 on maternal side
4 on both paternal
and maternal side
5 in patient's family
0 sex not recorded
1 male
2 female
3 both male and female

____

____

1, 3 Epilepsy
0 not recorded
1 no
2 on paternal side
3 on maternal side
4 on both paternal
and maternal side
5 in patient's family
0 sex not recorded
1 male
2 female
3 both male and female

____

____

1 Paroxysmal headache
0 not recorded
1 no
2 on paternal side
3 on maternal side
4 on both paternal
and maternal side
5 in patient's family
0 sex not recorded
1 male
2 female
3 both male and female

____

____

1 Other neurological disorders
0 not recorded
1 no
2 on paternal side
3 on maternal side
4 on both paternal
and maternal side
5 in patient's family
0 sex not recorded
1 male
2 female
3 both male and female

____

____

1 Endocrine diseases
0 not recorded
1 no
2 on paternal side
3 on maternal side
4 on both paternal
and maternal side
5 in patient's family

1 Allergic diseases
0 not recorded
1 no
2 on paternal side
3 on maternal side
4 on both paternal
and maternal side
5 in patient's family

____

1 Misuse of alcohol
0 not recorded
1 no
2 on paternal side
3 on maternal side
4 on both paternal
and maternal side
5 in patient's family

____

Suggested aetiological factors
2 Not known at all
? Hereditary factors
0 not recorded
1 no
2 yes
3 both hereditary and organic

1,2 Organic aetiology
0 not recorded
1 no
2 possible
3 probable
4 defined

Abnormalities of pregnancy
0 not recorded
1 no
Infection
Diabetes
Toxaemia of pregnancy
Imminent abortion
Medication during pregnancy
Other known

Abnormalities / delivery
3 0 not recorded
1 no
Caesarean section
Forceps delivery
Suction cup delivery
"Severe delivery"
Abnormal amniotic fluid
Umbilical cord complications
Other known

3 *Maturity of the newborn*
0 not recorded
1 premature
2 small for date
3 postmature

3 *State / the newborn*
0 not recorded
1 normal
Asphyxia
Apgar scores 7 r less
Defined hypoglycaemia
Abnormal icterus
Head pathology
Extracranial delivery injuries

Postnatal aetiological factors
0 not recorded
1 no
Meningo-encephalitis
Cranio-cerebral trauma
Hypoxia or anoxia
Defined hypoglycaemia
Intoxication
Other known

DATA CARD 2.

Identification
Neurological development
1 4 Gross motor
0 not recorded
1 normal
Spasticity
Tetraplegia dystonia
Hypotonia or ataxia or both
Clumsy gross motor movements only
Retarded gross motor development only
1 4 Fine motor-adaptive
0 not recorded
1 normal
2 abnormal
1 4 Language
0 not recorded
1 normal
? abnormal
1 4 Personal-social
0 not recorded
1 normal
2 abnormal
1 Intelligence development
0 not recorded
1 normal
2 deficient
3 mild retardation
4 grave retardation
6 profound retardation
1 Full scale intelligence quota
1 Trend of intelligence quota
0 not recorded
1 only one examination
2 rising
3 lowering
4 unchanged

Follow-up examination
3, 4 Gross motor balance
1 normal
2 abnormal
3, 4 Fine motor, coordination
1 normal
2 abnormal
3, 4 Language
1 normal

2 abnormal
3 4 Mentally
1 normal
2 abnormal

3 *Occasional seizures*
0 not recorded
1 no
2 yes
Febrile convulsions
C.N.S. infections
Breath holding spells
Hypoglycaemia
Hypocalcaemia
Acut. head trauma
Other known
1 2 Age at onset of occasional seizures
1 4 No. of occasional seizures

Recurrent seizures
1 2,3 Age at onset
1 2,3 Pretreatment duration of seizures
1,2 No. of pretreatment seizures
1 Frequency maximum of seizures
0 not recorded
1 less than one a year
2 approx. one a year
3 2—5 a year
4 6—10 a year
5 approx. one a month
7 approx. one a week
8 more than one a week

1 4 Frequency of seizures during the latest 12 months
0 not recorded
1 none
2 one
3 2—10 times
4 approx. one a month
5 2—3 a month
6 approx. one a week
7 more than one a week

1 4 Final remission from seizures
0 not recorded
1 no
2 below one year
3 below two years
4 below three years
5 3—5 years
6 5—7 years
7 7 years or more

1 4 Temporary remission
0 not recorded
1 never
2 below one year
3 below two years
4 below three years
5 3—5 years
6 5—7 years
7 7 years or more

1 4 Cluster occurrence of seizures
0 not recorded
1 no
2 infrequently
3 frequently
4 persistently

1 4 Status epilepticus
0 not recorded
1 never
2 one
3 2—3 times
4 4 or more times

1 4 Sleep-waking cycle
0 not recorded
1 waking state only
2 sleep state only
3 both sleep and waking state

1 Daily seizure maximum
3 Prodromal symptoms
0 not recorded
1 no
2 yes

3 Subjective initial symptoms
0 not recorded
1 never
2 predominantly motor
3 ″ sensory
4 ″ psychic
5 autonomous
6 ″ other which?

---

3 Objective initial signs
0 not recorded
1 predominantly motor
2 ″ sensory
3 psychic
4 autonomic
5 ″ other which?

1 4 Degree of disturbance of consciousness
0 not recorded
1 no
2 partial
3 both partial and complete
4 complete

3, 4 Tonic signs
- 0 not recorded
- 1 no
- 0 no plsthotonus
- 1 plsthotonus
- 1 right arm
- 2 left arm
- 3 both arms
- 1 right leg
- 2 left leg
- 3 both legs
- 1 right side of the face
- 2 left side of the face
- 3 both sides of the face

3 Clonic signs
- 0 not recorded
- 1 no
- 1 right arm
- left arm
- 3 both arms
- 1 right leg
- 2 left leg
- 3 both legs
- 1 right side f the face
- 2 left side of the face
- 3 both sides of the face
- 1 head, trunk

Adversive movements
- 0 not recorded
- 1 no
- 2 eyes turned to the right
- 3 eyes and head turned to the right
- 4 eyes turned to the left
- 5 eyes and head turned to the left

Other eye signs
- 0 not recorded
- 1 no
- 2 staring
- 1 blinking

Sensory signs and symptoms
- 0 not recorded
- 1 no
- 2 somato-sensory
- 3 other

Psychic signs and symptoms
- 0 not recorded
- 1 no
- 2 dreamy state
- 1 irritation
- 1 other

Autonomic signs and symptom
- 0 not recorded
- 1 no
- 1 discoloration of the face
- 1 salivation
- 1 enuresis, encopresis
- 1 nausea, vomiting
- 1 other

DATA CARD 3.

Identification

2 Oral automatisms
2 Behavioural automatisms
Other automatisms
Stereotypic movements
Jackson march
Myoclonic movements
Post-ictal signs and symptoms
- 0 not recorded
- 1 no
- 1 fatigue, sleep
- 1 amnesia
- 1 aphasia
- 1 confusion
- 1 post ictal paresis
- 1 headache
- 1 other

1 4 Number f seizure types
- 0 not recorded
- 1 one
- 2 two
- 3 three r more

Diagnosis f epilepsy

2 4 Partial cortical epilepsy
2 4 Psychomotor epilepsy
2 4 Secondarily generalized epilepsy
2 Petit mal epilepsy
2 4 Grand mal epilepsy
2 4 Infantile spasms
2 4 Akinetic-myoclonic epilepsy
2 Unclassified epilepsy

I vestigations

Bilateral symmetric cerebral involvement
- 0 not recorded
- 1 no
- neurological examination
- 1 EEG
- 1 PEG
- 1 cerebral angiography

1 brain scan
1 echo encephalography
1 other
1 1 2—3 investigations
2 4 or more investigations

Predominantly right side
cerebral involvement
0 not recorded
1 no
2 neurological examination
1 EEG
1 PEG
1 cerebral angiography
1 brain scan
1 echo encephalography
1 other
1 1 2—3 investigations
1 4 or more investigations

Predominantly left side
cerebral involvement
0 not recorded
1 no
2 *neurological examination*
1 EEG
1 PEG
1 cerebral angiography
1 brain scan
1 echo encephalography
1 other
1 1 2—3 investigations
1 4 or more investigations

1 Aetiological significance of
the findings
0 not recorded
1 no significance
possible
3 probable
4 defined

All EEGs of a patient normal
or borderline
PEG normal
Cerebral angiography normal

Medical treatment
1 *No. of seizures before treatment*
1 3 Duration of medical therapy
1 2, 3 Duration of phenemal therapy
Duration of phenytoin therapy
No medical therapy
Single anticonvulsant
1 phenemal
1 phenytoin
1 trimethadione
1 ethosuximide
1 sulthiam
1 acetazolamide
1 adrenocorticotropin
1 steroids
1 carbamazepine
1 other

1 4 Adequacy of medical therapy
0 not recorded
1 adequate
2 possibly inadequat
3 probably inadequate

1 4 Short term results of treatment
0 not recorded
1 good (seizures decreased
75—100 per cent)
2 moderat (seizures decreased
50—75 per cent)
3 bad (seizures decreased
0—50 per cent)

1 4 Long term result of treatment
0 not recorded
1 good (seizures decreased
75—100 per cent)
2 moderate (seizures decreased
50—75 per cent)
3 bad (seizures decreased
0—50 per cent)

Presenting side effect of medical
therapy
0 not recorded
1 neurotropic
2 dermatotropic
3 hematotropic
4 hepatotropic
5 gingivotropic
6 other
Intoxication of anticonvulsant

DATA CARD 4

Identification
Seizure provoking factors
2 0 not recorded
2 1 acute febrile infection
2 1 sleep deprivation
1 fatigue
1 photic stimulation
1 menstruation
1 psychic tension
1 irregular meals
1 other

1 Duration f seizure illness
- 0 not recorded
- 1 below one month
- ?—3 months
- 3 3—6 months
- 4 6—12 months
- 5 1—2 years
- 6 2—3 years
- ~ 3—5 years
- 8 5—‹ years
- 9 years or more

Behavior

3,4 Presenting neurotic problem
- 0 not recorded
- 1 no
- ˍ anorexia nervosa
- 3 obesity
- 4 nail-biting
- 5 enuresis, encopresis
- 6 other

3,4 Presenting psycho-neurotic problem
- 0 not recorded
- 1 no
- 2 phobia
- 3 anxiety
- 4 obsessive movements
- 5 hysteria
- 6 tic
- 7 depression
- 8 other

3,4 Presenting psychotic problem
- 0 not recorded
- 1 no
- 2 autism
- 3 symbiosis
- 4 other

3,4 Hyperkineti syndrome
Adjustment difficulties
Specific reading and writing difficulties

1 Organic background f psychopathology
- 0 not recorded
- 1 no
- 2 possible
- 3 probable
- 4 defined

1 2, 4 *S hool education*
- 0 not recorded
- 1 not yet mature for school
- 2 started primary school
- 3 completed primary school
- 4 started commercial school
- 5 completed commercial school
- 6 started middle school
- ~ completed middle school

1 2, 4
- 1 started high school
- ? passed high school examination
- 3 started college
- 4 completed college
- 5 started university studies
- 6 completed university studies
- ~ other school education

1 2, 4 Special education
- 1 special class
- 2 class for mildly mentally retarded
- 3 training school
- 4 other
- 5 no school education

1 2,3,4 School improvement (Scale 5—10)
- 0 not recorded
- 1 mean below 6
- ? mean 6—7
- ? mean ~—8
- 4 mean 8—9
- 3 mean 9—10

Occupatio

1 2,3 Occupation f patient (16 or more)
- 0 no occupation
- 1 Rauhala s class 1
- 2 " "
- 3 3
- 4 " 4
- 5 5
- 6 6
- 7 7
- 8 8
- 9 9

Employability

1 Main type of activity
- 0 not recorded
- 1 employed
- 2 students and school children (15 years r more)
- 3 members f family
- 4 pensioned, those without occupation
- 5 institutionalized

1 Economical activity
- 0 not recorded
- 1 employed

2 temporarily unemployed
3 chronically unemployed
4 working in household at home
5 compulsory military service
6 attending school
7 chronically unfit for work
8 other activity

1 Main source of livelihood
0 not recorded
1 employment
2 pension
3 social relief, loan or scholarship
4 capital or interest
5 income or property of another person

1 Capacity for work
0 not recorded
1 complete capacity
2 decreased capacity 0—50 %
3 50—75 %
4 more than 75 %

1 Disadvantageous influence on housework, school or occupation
0 not recorded
1 no influence
2 slight to moderate
3 marked
4 completely unable to work

Psycho-social adjustment
1 Activities of daily living
0 not recorded
1 complete capacity
2 partial capacity
3 no capacity

1 Social quota
1 Personal independence
0 not recorded
1 completely independent
2 slightly to moderately dependent
3 greatly dependent
4 completely dependent

1 Capacity for inter personal contacts outside the home
0 not recorded
1 no contacts
2 infrequent contacts
3 moderately frequent contacts
4 frequent contacts

1 Compulsory military service (males 19 years or more)
1 no
1 qualified
2 partially unqualified
3 temporarily unqualified
4 terminally unqualified

1 Driving licence (18 or more)
0 not recorded
1 no attempts to obtain it
2 no licence despite attempts to obtain it
3 licence withdrawn
4 owner of licence

5 Marital status (17 or more)
0 not recorded
1 married
2 unmarried
3 widow(er)
4 separated
5 divorced
6 engaged

1 Use of alcohol of patient
0 not recorded
1 no
2 below ½ litre a month
3 ½ litre or more a month

Socio-economic status of patient
0 not recorded
1 employer
2 owner of private enterprise
3 higher official
4 clerk
5 skilled worker
6 unskilled worker
7 pensioned
8 other

1 Occupation of guardian
0 not recorded
1 Rauhala class 1
2 " 2
3 " 3
4 " 4
5 " 5
6 " 6

7 7
8 " 8
9 9

Guardian if not the two biological parents
- 0 not recorded
- 1 divorced parent
- 2 unmarried parent
- 3 adoptive parents
- 4 foster parents
- 5 other

1 Attitude of the environment
- 0 not recorded
- 1 positive
- 2 lternating positive and negative
- 3 indifferent
- 4 somewhat negative
- 5 definitely negative

1,5 Tenure status f conventional d elling of patient's family
- 0 not recorded
- 1 owner of the house
- 2 owner of the flat
- 3 off cial residence
- 4 lodger

Type of house
- 0 not recorded
- 1 own house
- 2 row house
- 3 block of flats
- 4 farm house
- 5 other

1 Type f kitchen
- 0 not recorded
- 1 kitchen
- 2 kitchenette
- 3 neither

1 2,3,4 Total no. of rooms
1 2,3,4 No. of residents in the dwelling

1 5 Facilities of the dwelling
- 0 not recorded
- 1 sewage drain
- 2 water conduit
- 3 water-closet
- 4 central heating
- 5 warm water
- 6 bathroom

Dem graphic and physical growth data

1 ,3,5 Birth order
1,2,3,5 Total no. of children in patient's family
2 Handedness
- 0 not recorded
- 1 right-handed
- left-handed
- 3 ambidextrous
- 4 indefinable

1 2,3,5 Height on initial examination
1,2,3,5 Weight on initial examination
1 2,3,5 Head circumference on initial examination
1,2,3 Age at initial examination
1 2,3,5 Height on foll w up examination
1,2,3,5 Weight on f llow up examination
1,2,5 Head circumference on f llow up examination
1,2,3 Age at follow up examination
1 2,3 Age at menarche
1,2,3 Interval between patient and preceding delivery

3,4 *Died*
- 1 no
- 2 yes

APPENDIX II

Analysis of EEG

Figures before the pairs of numbers refer to tests mentioned in Appendix I

Tests *Identificatio*
No. of FEG card
Date of recording FFG

1 4 *D gree of abnormality n FFG*
00 normal
01 borderline
02 abnormal
03 markedly abnormal
04 uncertain

General pattern
05 flat
06 neonatal acti ity
2,3 07 hypsarrhythmia
08 disorganized tachy or bradyrythmia
09 persistent delta activity
10 persistent SpW activity
11 persistent sleep activity
12 persistent hemispheric asymmetry
13
14

Occipital hythmic act vity
2 15 regular
2 16 irregular
17 slow (for age)
18 no rhythmic activity

Other rhythms
19 mu rhythm
20 s ow occipital rhythm
21 other known rhythm

Beta activity
22 marked, diffuse
23 marked frontal

Slow (theta-delt) am rphous diffuse background act vity
24 normal
4 25 increased
26

Non-irritat focus asymm try
3 27 defined irregular persistent delta activity
28 intermittent slowing
29 local low amplitud activ ty
30 other known

Irritat r focus asymm try
3 31 spikes
32 sharp waves
33 SpW complexes
34 various foci or asymmetries
35 a ymmetric spik discharges
36 6 and 14 Hz positiv spikes
37 other

Attrib tes of the pairs f n mbers 15—31 (not 18)
1—3 localizing code
4 0 = amount not determined
1 = slight
2 = moderate
3 = marked
5—6 *frequency minimum*
00 = not defined
7 *eye open g-closing*
0 = reaction not determined
1 = no reaction
2 = slight reaction
3 = defined reaction
8 *significant asymmetry*
0 = no asymmetry
1 = asymmetry on the right
2 = asymmetry on the left
3 = side of asymmetry not determinable

Attrib tes of the pairs of numbers 27—37
1—3 localizing code
4 *0 = amount not determined*
1 = one
2 = a few
3 = marked, frequent
4 = persistent

5 *Stat of maximum frequency*
0 = n t determined
1 = relaxed waking state
2 = eye closing (off" reaction)
3 = intermittent photic stimulation
4 = hyperventilation
5 = drowsiness
6 = sleep
7 = d fferent activating factors

1 3 *N n-specific paroxysms*
38 delta
39 theta-delta

40 theta
41 fast
4_ other

1 4 *Specific bilateral paroxysms*
43 6 Hz SpW
44 regular bilateral synchronous three Hz SpW
45 irregular SpW
46 poly SpW
4 less than 2½ Hz SpW
48
49

Abnormal feat res f sleep activity
50 asymmetric spindel activity
51

Attributes to the pairs f numbers 33—51
1—3 localizing code
4 0 = am unt not determined
1 = one
2 = a few
3 = marked
4 = persistent
5 *state of maximum frequency*
0 = not determined
1 = relaxed waking state
= eye closing (ff" reaction
3 = intermittent photic stimulation
4 = hyperventilation
5 = drowsiness
6 = sleep
7 = different etivating fact rs

6 *relationship to cli ical manifestations*
1 = latent
2 = associated with seizure
3 = both associated and unassociated with seizure

Changes of the success ve records
52 bilateral diffuse abnormality disappeared
53 bilateral diffuse abnormality decreased
54 bilateral diffuse abnormality increased
1 55 non-irritative focus disappeared
56 non-irritative focus decreased
57 non-irritative focus increased
1 58 non-irritative general paroxysms disappeared
59 non-irritative bilateral paroxysms decreased
60 non-irritative bilateral paroxysms increased
1 61 irritative focus disappeared
62 irritative focus decreased
63 irritative focus increased
1 64 epileptic paroxysms disappeared
65 epilepti paroxysms decreased
66 epil ptic paroxysms increased
67 qualitatively new abnormality
68 changed localization of abnormality
69 other change

Abnormal EEG f relatives
70 in patient's family
71 in relatives

Fig ( ) Localization code

	Fp1		Fp2			2									
F7				F8			4	22		22		22			
	F3	F	F4		020	3			33		66				
T3	C3	Cz	C4	T4	030	5	6	56					88		
	P3	Pz	P4		040	7				44					
T5				T6			8		55			77			
	01		02			9		9		9	9				

In *Fig* (a) the key for use of the localization code is presented. To the left there is an international 10—20 system of electrode placement and in the middle of the figure the sites of electrodes on the right side of the skull are numbered (from 2 to 9). Similarly the numbers correspond to the sites of electrodes on the left side. To the right of the figure larger areas than the point of one electrode are shown with pairs of numbers.

The localization of an abnormality is always shown with a three-numbered figure. Symmetric bilateral findings are demonstrated with numbers between the same transversal lines. Asymmetric findings are shown in two ways: when the finding is on one side only the reciprocal location on the other side is marked with 0 in the three numbered localization figure. Instead of 0 number 1 is used when there is a lateralization of an abnormality.

Examples
656 = symmetric bilateral centrotemporal
140 = asymmetric frontotemporal with lateralization to the right
840 = asymmetric left hemisphere only
090 = symmetric middle frontal
481 = asymmetric lateral frontopostero-temporal with lateralization to the left

In the present study however the following simplified system of areas was applied: frontal, central, posterior, ant. temporal, mid temporal, post. temporal, right half, left half and both halves.

APPENDIX III

Numbers of diagnoses used while looking for case records

(According to International Classification of Diseases and Causes of Death accepted by WHO 1948, Finnish translation 1953)

010	253	344	781
023	290	351	782
020	325	352	792
040	330	353	800

096	331	355	801
122	332	377	802
193	333	483	803
204	334	750	85
223	340	760	853
228	341	762	854
237	342	769	855
271	343	780	

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BY JÖRGEN SILWER

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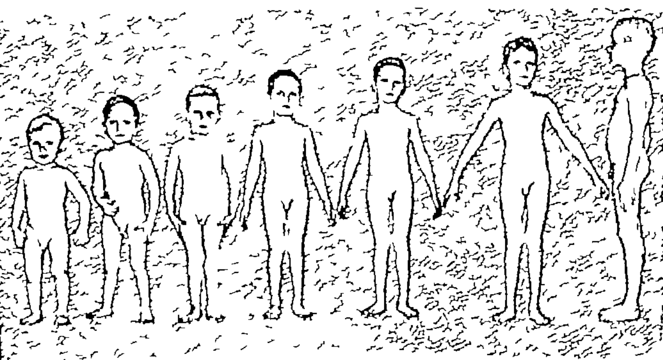
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SUPPLEMENT [illegible]

A PROSPECTIVE LONGITUDINAL STUDY OF CHILDREN

DATA ON PSYCHIC HEALTH AND DEVELOPMENT UP TO 8 YEARS OF AGE

BY GUNNAR KLACKENBERG



From the Pediatric Department of Karolinska Institutet at Karolinska sjukhuset, Stockholm, Sweden. (Head: J. Lind)
and the Pediatric Department of the University of Göteborg at the Children's Hospital, Göteborg, Sweden. (Head: P. Karlberg)

A PROSPECTIVE LONGITUDINAL STUDY OF CHILDREN

Data on psychic health and development up to 8 years of age

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This prospective study of children would never have materialized without the interest in the child as a whole which my clinical teacher Professor emeritus Arvid Wallgren has displayed. He has been extremely patient his endurance has been stimulating and his confidence a strength for me I am most grateful

Similarly I am indebted to Professor John Lind for the many ways in which he has supported and enthusiastically encouraged the work as well as for providing facilities for the study in his capacity as head of the Department of Pediatrics at Karolinska Sjukhuset

The many years required for a longitudinal study of growth carried out under uncertain financial conditions form a good test of the durability of the team that started the project I am therefore very pleased to note that the five people who began this work sixteen years ago are still on the job My deep thanks are chiefly due to the four original colleagues who have invested a great deal of emotional capital in the study With his clearsightedness helpfulness and eye for essentials Professor Petter Karlberg has been a source of inspiration all along for the study as well as for me personally Our psychologist Ingrid Klackenberg-Larsson and our pediatrician Henrik Lichtenstein have for many years undertaken the continual task of collecting psychic and somatic data in a matter-of-fact perceptive and knowledgeable manner It has been a pleasant experience to survey all the exact and concrete observations which have been noted in case records and computer cards and which form a foundation for this thesis I have further reason to thank my sister Ingrid Klackenberg-Larsson for the valuable criticism and discussions that have arisen out of her scrutiny of the manuscript

Our nurse Inga Svennberg has been most tactful and friendly in her handling of contacts with children and relatives Her ability to keep things running has been valuable for the study and for me

During some of the years when data were being collected for this work other persons with a psychological training also made valu-

able contributions It is a pleasure for me to mention the assistance provided by fil lic Jan Stensson over a series of years

Professor Ingvar Johannesson and Ass Professor Inga Engström have placed their knowledge at the disposal of the study for several years and I should like to thank them for the conversations and exchanges of opinion which have enriched my work.

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During the last few years the processing of data has been undertaken in a most considerate manner by Mr Thorvald Landström at Göteborgs Universitet I am grateful for his help

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CONTENTS

INTRODUCTION

For many years now longitudinal prospective studies of growth co-ordinated by Centre international de l enfance (C I E.) have been conducted in London Paris Brussels Zürich and Stockholm (Solna) whereby development behavioural and somatic growth data are recorded for child samples at various stages on uniform lines and using the same methods Continual comparable data for the first years of life have also been obtained from children in two African centres (Kampala and Dakar)

Before venturing on extensive international comparisons on the requisite scale of the growth norms of upbringing and development characteristics of children from different cultural environments it has been essential for the various national centres to analyse the host of information collected over the years in various quarters. The present study is mainly to be regarded as part of this effort to begin by penetrating our own results

This report on the longitudinal Stockholm study comprises an analysis of part of the psychosomatic data collected during the first eight years of the children s lives The object is to examine the development of certain habits incorporated in the child s adjustment as it grows up Comprehensive structured interviews with mothers assessments of the child and a variety of tests administered at regular intervals are used to illustrate the stability of skills developed, together with the considerable variations between individuals of the same age Pride of place is given in this study to the mutual relationships between different behavioural variables and between those variables and various kinds of environment The development of the behavioural characteristics chosen for analysis is described against the background of a large variety of social factors The child s somatic state of health has also been included as a background factor where applicable

The present report forms part of a series of published or scheduled essays on child development The aims and general structure of the project have already been presented in Acta paed. scand. 1968

suppl 187 The same issue also included a number of essays containing social somatic and psychic data from the first three years of the children s lives The eight papers presented here should be viewed in conjunction with six published previously (four in the abovementioned Acta paed. supplement one in Journal child psychol and psychiat 1965 one in Human Biology 1966)

CHAPTER I

LIST OF THE PAPERS COMPRISING THIS THESIS

1 The development of children in a Swedish urban community A prospective longitudinal study Introduction, design and aims of the study Description of the sample
Karlberg P Klackenberg G Klackenberg-Larsson I, Lichtenstein H. Stenson J and Svennberg I (Summary page 12)

2. The social and family background and its changes during the childrens first three years of life
Klackenberg G Karlberg P Klackenberg-Larsson I, Lichtenstein H. Stenson, J and Svennberg I. (Summary page 13)

3 Breast-feeding and weaning: Some social psychological aspects
Klackenberg G and Klackenberg-Larsson, I. (Summary page 29)

4. The sleep behaviour of children up to three years of age
Klackenberg G (Summary page 29)

5 Some differences in infant feeding and elimination training in five European longitudinal samples
J child psychol and psychiat 6: 179-201 1965
Hindley C Filliozat A.M. Klackenberg G Nicolet-Meister D Sand E.A. (Summary page 30)

6 Differences in age of walking in five European longitudinal samples Human Biology 38: H: 364-379 1966
Hindley C. Filliozat A.M. Klackenberg G Nicolet-Meister D Sand, E.A. (Summary page 31)

7 Non-nutritional sucking in ages from infancy up to 8 years of age
Klackenberg G

8. Nailbiting
Klackenberg, G

9 Rhythmic movements in infancy and early childhood.
Head-banging head-turning and rocking
Klackenberg G

10 Expectations and reality concerning toilet-training
Klackenberg G

11. A prospective longitudinal view of early speech impediments
in a normal child sample
Klackenberg G

12. Further studies of sleep behaviour (principal ages 4 – 8 years)
Klackenberg G

13 Temper tantrum and destructiveness
Klackenberg, G

14 Tics in statu nascendi
Klackenberg G

15 Symptom changes and symptom load.
Klackenberg G

CHAPTER II

THE STUDY ORGANIZED AS TEAMWORK - THE TEAM

The Swedish study initiated by Arvid Wallgren was planned in the autumn of 1954 when Petter Karlberg now Professor Karlberg and I attended the first Annual Growth Meeting of the C I E. in Paris During the winter we were joined by a psychologist I. Klackenberg-Larsson, and a pediatrician Dr Henrik Lichtenstein, and set about planning the Clinic for the Study of Children s Development and Health which was established in January 1955 at the Department of Pediatrics at Karolinska Sjukhuset A nurse L.Fremberg joined the team at that time.

These five persons have been engaged in the work from the start and are still participating.

As the volume of work increased with the inclusion of additional children over a three-year period it became necessary to obtain further assistance with the collection of all the data. Consequently the following persons have been associated with the study at times in the period covered by the present thesis

B. Olofgörs psychologist	1/3 1958 - 28/2 1959
K. Widström,	1/2 1959 - 31/3 1960
J Stensson,	1/4 1960 - 1/9 1967
B. Kellbom	1/4 1963 - 31/5 1964

In 1963 Ingvar Johannesson, now Professor Johannesson, joined the team and with his colleagues is following up the children in the school situation.

Since 1965 Assistant Professor Inga Engström has been helping with the future design of the study

CHAPTER III

SUMMARIES OF PREVIOUSLY PUBLISHED PAPER 1 AND 2 IN ACTA PAED. SCAND 1968 SUPPL. 187

Paper 1. Introduction, design and aims of the study. Description of the sample.

The Stockholm study the first prospective longitudinal study of child development and health in Sweden is presented and its objectives and intended design discussed. Of the sample of 212 children 14 % were recruited from an obstetrical clinic and 86 % by an invitation to every fourth pregnant woman at the Solna maternity welfare centre to participate in the study In the event of anybody invited to participate being prevented from doing so the invitation was passed on to the fourth next mother Only 3 % of those originally approached considered themselves unable to participate

The two recruitment procedures resulted in two samples of different sizes which were later amalgamated after analysis and comparisons to form the basis of the study Socio-economically the total group represents a truer picture of the community from which it has been drawn than does the maternity welfare centre group alone Insofar as comparisons have been possible with known conditions in the recruitment area, which is part of Greater Stockholm the sample has in most respects agreed well not only in terms of social class distribution but also in terms of the age distribution of the mothers the proportion of children born out of wedlock, the proportion of children conceived out of wedlock and the distribution of children by order of sequence gestation period and weight at birth.

The number of boys (122) which in spite of the antenatal recruitment was unexpectedly large in relation to the number of girls (90) was not statistically unacceptable from the point of view of sampling A t-test showed that the probability of such a random distribution exceeded 5 %.

In view of the recruiting methods employed together with the established similarities between the sample and known conditions in the

Stockholm area we have found it probable and have assumed by way of a working hypothesis that the sample represents not only itself but also a wider area, a Swedish city community

Paper 2. The social background and its changes during the children s first three years of life

The composition and social background of the families participating in the study are analysed with regard to a number of important variables: housing conditions education occupation income size of family age of parents and marital status The families are distributed throughout the social scale in a manner representative of Stockholm.

A new international system of social classification devised by Graffar was employed parallel to the Swedish occupational system. According to Graffar s system which takes into account housing conditions education occupation and income on five-point scales a family is socially characterized by a social score of between 4 and 20 All the variables in the grouping system except education are on the whole normally distributed. The mothers gainful employment its incidence and stability are given particular attention as an important background factor during the children s first years of life

The average social standard of the families improves during the children s first three years of life Overcrowding which is considerable when mother and child return home from the maternity hospital declines appreciably during the first years The families incomes have improved. In all probability the changes for the better which can be discerned through Graffar s system of points reflect the general rise in social stabdards in Sweden during these years especially as regards the social stabilization undergone by the youngest families.

CHAPTER III

S U M M A R I E S O F P R E V I O U S L Y P U B L I S H E D P A P E R 1 A N D 2 I N A C T A P A E D S C A N D 1968 S U P P L. 187

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. of informa- and examina- is done	Age at investigation: Ante-natal	lying in	1	3	6	9	12	18	2	3	4	5	6	7	8
			months						years						
ings			x	x	x	x	x	x	x	x	x	x	x	x	x
ld by psychologist											x				
her															
itude-scale															
aeffer and Bell											x				
- mother											x				
father															
A															
ructural interview ncerning health and imentation form II			x	x	x	x	x	x	x	x	x	x	x	x	x
inical examinations form II			x	x	x	x	x	x	x	x	x	x	x	x	x
matic measurement form III			x	x	x	x	x	x	x	x	x	x	x	x	x
nd, knee X-ray			x	x	x	x	x	x	x	x	x	x	x	x	x
OCIAL CONDITIONS form 0							x		x	x	x	x	x	x	x
ocial chart 1-3 yrs (longitudinal)										x _					

The data on which the results presented here are principally based are taken from the structured interviews Brunet-Lezine and Terman-Merrill development and intelligence tests have been used to elucidate the relationships to different behavioural variables The relations to the various personality tests will be dealt with in later reports. Evaluation of these tests is not yet complete The child psychologist s assessment of the child in different variables on a five-point rating scale has been utilised for certain development characteristics Similarly the clinical findings of the pediatrician have served as a background. The various data in the comprehensive social questionnaire have been used to illustrate the argument throughout

Each of the three interview forms (four at 4 - 5 years) concerning the child s behaviour in general and in special circumstances (e g separation from the home accidents illness etc) contains 60 items These forms are designated V VI VIII and IX (the last not used here) The alternative answers are rarely confined to a categorical "yes or no Usually the mother being interviewed has been offered a range of alternative answers enabling her to make graded or qualified statements concerning the child s symptoms together with their frequency and duration Appendix 1 contains the items used as material and forming the basis of the essays in this report The complete questionnaires forming the basis of the international part of the investigation are given in A base-line of investigations for longitudinal growth studies of the child (Falkner 1955)

Owing to the financial considerations dictated by the time-consuming *investigations data were collected at the age of 6 years and* above partly with the aid of a questionnaire sent to the mothers homes When the child and its guardian visited the clinic for examination the questionnaire was completed by the psychologist In addition to this supplementary check a brief structured interview was held on certain selected items This difference of procedure in the collection of data at ages before and after six years has in a way impaired the continuity of the investigation One can only speculate as to the extent to which it has also affected the result Many items are of such a kind that the deviant symptomatic manifestations have the same chance of being noted regardless of the circumstances while others are liable to be given another emphasis by the mother when she is alone than when she is guided by questions from the trained specialist For further details the reader is referred to the selection of questions used at 6 - 8 years given in Appendix 1

CHANGES IN THE COMPOSITION OF THE SAMPLE UP TO 8 YEARS LOSSES FROM THE SAMPLE.

There are great difficulties and risks involved in a longitudinal study extending up to the age of 18. Apart from the financial hazards there is the risk of invested capital failing to give a sufficient return owing to drop-outs from the sample The objective of recruitment is to obtain a sufficiently large representative sample to facilitate reasonably reliable statistical computations Once this has been achieved, it is necessary to maintain the subjects motivation to participate If a family moves away from the site of the investigation their continued participation will probably stand or fall by the distance they now have to travel from home Continued participation is accepted even if a child moves to a different geographical environment from its original metropolitan surroundings which has occurred in a few cases The present investigation has been favoured by the relatively generous employment opportunities of the metropolitan area coupled with the congested nature of the housing market It is much easier to keep the families interested if contacts and investigations at the clinic are always handled by the same staff These conditions have fortunately been satisfied in the Stockholm study thus making it possible to preserve the continuity of assessments to a very great extent

A certain drop-out is inevitable No continual long-term investigations of this kind, representatively recruited from different levels of society have yet been published without reporting a heavy drop-out (1) If the people who drop out do so because they move far away from the place where the investigation is being conducted, this can be regarded as a random circumstance although socially speaking it can lead to a skew distribution of the sample A more severe loss is sustained from the point of view of evaluation of the results obtained and the probable general validity of those results when a family stops participating for lack of interest This may conceal difficulties which have arisen in balancing the domestic emotional situation. The people concerned do not want to have their children exposed unnecessarily by detailed studies nor do they themselves want to be provoked by interviews Motivations to this effect are seldom ex-

pressed so explicitly as this would suggest In various connections however one can discern something of the true reason for discontinuation. This reduces the available basis for symptom frequencies and etiological symptom studies. An attempt is made below to elucidate the causes of the - fortunately - small losses occurring in this study

At the conclusion of the random recruitment the sample amounted to 212 cases During the period up to and including 8 years covered by this report 12 children, i e 5 6 % of the original number had definitely ceased to participate in the study Of these 7 are girls and 5 boys with the result that the numerical superiority of the boys has become even more pronounced than it was at the beginning of the study

The final investigations of those who have dropped out of the study occurred at the following ages and for the following reasons

Last investigation at	No	Cause Removal	Death	Psychic reasons lack of interest
12 mths	2	2		
18	1	1		
36	4	1		3
48	2			2
60	1	1		
72	2	1	1	

Thus half of the twelve have moved to remote areas of Sweden or abroad. One boy was killed in a road accident at the age of 6 This leaves 5 children (3 ♂ + 2 ♀) who for various reasons have not been willing to continue after the age of 3 - 4 One mother (belonging to Jehovah s Witnesses) gave reasons of religious principle Another declined to give any reason; there was nothing exceptional about the development or behaviour of her child. In the three remaining cases the inconvenience entailed by the extensive investigation was said to be so great that the parents wished to withdraw Two of these children were so noisy and restless when they were being examined

that the mothers found this among other things a strain. Despite intensive efforts to induce the mothers to change their mind, contact had to be discontinued. Finally one boy suffered from synostosis cranii with obvious mental retardation. Since he was frequently in hospital the mother considered these investigations sufficient There seemed little point in retaining the boy in a so-called normal child sample since the deviation was clearly pathological

This slight drop-out affected all social groups Changes in the percentage distribution according to the Graffar five-point scale are not more than 1 % in either direction. Far greater than these changes in registered social group status is the rise in social standards undergone by the group during these 8 years which reflects percentage differences of up to 20 %.

Only one of the 12 children ceasing to take part in the study was born out of wedlock. Thus the drop-out from the 23 children born out of wedlock who were originally recruited was proportionally the same as for the sample as a whole The educational level of the group of mothers who have ceased to take part in the study corresponds very closely to that which is representative of the original sample

Conclusion. The drop-out from the sample during the first eight years of the children s lives has only to a minor extent been due to lack of interest on the part of the mothers Nor has it resulted in any notable changes in the social composition of the sample

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CHAPTER VI

ADVANTAGES AND DISADVANTAGES OF DIFFERENT WAYS OF DATA-GATHERING

Aspects of longitudinal versus cross-sectional studies

Prospective or anterospective longitudinal studies with reference to child health and development are here taken to imply that the same individuals are continually observed in adequate studies or behavioural assessments at regular intervals during their childhood. The intervals between studies will vary according to the changes in development which are to be investigated and according to the ages of the children. The more rapidly a development trait a skill a characteristic or a bodily measurement changes the more frequently studies should be made to investigate the growth pattern. If a longitudinal follow-up is to be a practical proposition it must also take into account the visiting frequency for which parents and children can be motivated Another limitation is imposed by financial considerations A project which sets out to trace individual progress from birth to adulthood is bound to be expensive and the scientific return must be reasonable in proportion to the financial outlay

A great deal of the knowledge of child development has been derived from cross-sectional investigations of representative samples from different age groups Thus the data obtained on different occasions have not originated from the same children but from groups of different children at different ages A cross-sectional study takes far less time Results are obtained in proportion to the immediate work input and are not affected by the time which elapses before the individual child attains maturity It is invariably easier to obtain fully representative samples in cross-sectional investigations where drop-outs can be compensated by new recruitment In some respects however the cross-sectional investigation is inferior to the longitudinal follow-up When studying relations between previous observations and subsequent events with a view to constructing a model for prediction the only resort is continual observation of the phenomenon to be studied.

A child's mental and bodily development proceeds uninterruptedly but by no means in a straight line. Periods of rapid development alternate with periods of steadier progress. Children attain these periods at different ages. Consequently a cross-sectional investigation of children of a certain age yields data from children at different stages of development, with the result that there is generally a great deal of variation in any single age group. Practically any behaviour can appear normal. A bodily measurement or a behavioural characteristic can be accommodated within the normal deviations afforded by the cross-sectional investigation; at the same time as the development of the individual child at the age in question may deviate from the optimum rate of development for which it is genetically programmed. The principal of the longitudinal follow-up, which is gaining increasing practical currency in connection with preventive child care, is that progress, regression or deviant development at certain ages is assessed in relation to the initial situation together with achievements during earlier stages. Knowledge of normal long-term development, symptom variation and symptom persistence is essential for an adequate assessment of the value of current observations concerning the individual child.

Data concerning sleep are a case in point. We know from cross-sectional figures that a fairly high percentage of children at different ages wake up night after night or at least sleep for only a few hours at a time. But these figures do not tell us whether it is the same children who deviate in the various age groups, in other words whether sleep disturbances or small sleep requirements are a characteristic development pattern in certain children or merely a temporary phenomenon. Thus longitudinal studies of a representative number of children provide a more reliable frame of reference for the decisions that have to be taken daily by pediatricians and child psychiatrists.

Aspects of the use of prospective versus retrospective data in everyday and scientific work

In locating the cause of a behaviour use is always made in clinical work of the anamnestic data which parents are able to provide The case history plays a major part in the diagnosis The therapeutic measures taken are related to these data as well as to what has been revealed by the investigations If records are not available from the child s earliest years the parent s memory observance and even their interpretations will be important for diagnosis and treatment Consequently clinics are often consigned to the use of available retrospective data This is a necessary resort which judiciously applied can produce satisfactory results

Retrospective data have also been frequently used in scientific investigations The mother s recollections are recast in the form of facts In these contexts reliability is of the utmost importance Investigations of the selective and incomplete manner in which memory functions have cast doubt on certain retrospective data which should accordingly be used with care

Pyles et al (3) found on comparing antero- and retrospective data from the longitudinal Berkely study that even when their children were no more than 21 months old, mothers could give a reliable statement of their weight at birth but had often forgotten important details concerning their own state of health during pregnancy as well as facts connected with their deliveries The same uncertainty surrounds conclusions on the psycho-motoric development of children based on recollections several years later (2) Chess et al (1) noted from their experience of the longitudinal New York investigation that as regards the development of behavioural problems significant distortions in development reporting had arisen in one third of the cases within the space of a few years They also point out the risk of certain parents attempting to force their recollections of behavioural development into generally accepted theories of cause and effect "The danger of such a self-fulfilling prophecy should lead to careful scrutiny of retrospective behavioural data when the nature of recall could be influenced by the knowledge of the theory" Robbins (4) alludes to similar hazards in the use of retrospective data concerning child handling methods

when he concludes: As a result there may be a self-perpetuating 'validation with experts opinion influencing parental reports which in turn influence the experts"

For the above reasons the prospective method of investigation must be superior to the retrospective But the prospective investigation is also based upon the memory of the observer although a far shorter memory is called for so that the facts obtained are more reliable In the present study the interval between the collection of facts varies from one to three months during the first year of life up to six months during the second year and up to 12 months subsequently More frequent investigations are again conducted during puberty with regard to certain data. Moreover much of the data on which investigations of behaviour are based are on-the-spot observations made in connection with the investigation itself

Validity and reliability of reported observations

One important question concerns the validity of the observations reported. It is of course the mother who is best acquainted with the child s behaviour Longitudinal investigations are practically impossible if the demands of science include that a trained outside observer be continually at the child s side Sources of error are reduced by the detailed psychological and somatic investigations recurring at regular intervals together with the mother s structured interview statements This is particularly true of reports concerning factual events (e g accidents periods in hospital or children s homes social data) or striking behaviour (e g motoric skills speech defects tics rhythmic movements bedwetting daytime wetting etc) The assessment of expressions of feelings involves a larger element of subjective evaluation, since the norms concerning what is great and small are dependent on the experience mood and temperament of the observer Parents have no uniform scale of measurement for the temperature of an emotional climate nor have they any calibrated dimensions to indicate the degree of aggressiveness or sensitivity As far as interviews are concerned, we are confined to the views expressed by a parent according to his or her individual frame of reference The interviews included to afford certain opportunities of measuring expressions of feelings in exampli-

fied behaviour per unit of time or more generally by expressions such as "usually" often sometimes seldom" or never" In this way the gradation represents a differentiation which brings out certain important differences Clearly a child that throws itself on the floor every day in rage or despair exhibits a symptom of its feelings more intensively than another child who reacts in the same way about once a month.

In all respects efforts have been made to obtain data which as far as possible are referable to factual descriptions rather than interpretations and evaluations A similar procedure has been validated in the longitudinal New York investigation by mutually independent outside psychologists carrying out a number of assessments of the child s behaviour and noting their observations for comparison with the mother s statements (5) The result of these comparisons was that each of the direct observations agreed with the parent interviews at a probability level of 01

One weakness revealed in the long-term comparison of certain kinds of behaviour is that the interview question may have been phrased somewhat differently at a later stage than during the first five years Even if the principal content is the same a different shade of meaning can result in a different gradation especially if the scale has been given another name This is illustrated by the question on night waking Up to 5 years the mother was asked: "Has he/she woken up during the night since last time? The alternative answers which the psychologist had to choose from were distributed on the scale: nightly several times nightly once 3 - 6/week, 1 - 2/week less never At 6 - 8 years the question read: "Has he woken up at all during the night? The alternative answers: always often sometimes seldom, never The six points of the scale reflecting different frequencies of sleep disturbance during the first five years of life are readily transformed into five (nightly several + nightly once = nightly) But the question is whether this corresponds to always in the alternative answers for the subsequent years Obviously if a child wakes up every night it satisfies the parent s criterion of always But this may also include a somewhat lower frequency than the nightly one The boundaries between always often and sometimes are less definite

than the attempts at gradation by unit of time which were used during the preceding years

There is little danger of missing trends towards changes in individual or group behaviour from one year to another A five-point or in exceptional cases three-point scale will in all probability reveal palpable differences by a scale discrepancy of two points or more even if the assessment is made at yearly intervals Thus according to our assumption each child is characterized by the position it occupies on the scale or by the position next to it In an investigation covering several years there is bound to be a risk of questions and answers acquiring a somewhat different emphasis from what was originally the case

The children in this longitudinally followed up sample were not treated at the clinic nor have their parents received any special guidance; like other parents they have had to consult the regular medical and child guidance facilities or a private doctor if they have felt this to be necessary For obvious ethical reasons the investigation team could not stand idly by if diseases were diagnosed or serious deficiencies revealed. In such cases the parents have been given help in establishing the contacts which have been thought necessary and which they themselves have wished for The primary task however has been the continual accumulation of data from sufficiently related points in the child s development In this way the children and parents have come to form a special group the object of friendly and very close interest It is hard to say how far this has resulted in a different parental attitude towards the children from what would normally have been the case Interviews may conceivably arouse second thoughts which in turn may develop into reflection and ripen into wisdom. In this way the unreflecting parent may become more aware of the problems involved. Few peopl are entirely unaffected by a detailed neutral interview concerning a child s behaviour It is impossible to say to what extent unintentional influences occur in a longitudinal investigation or what the nature of such influences would be In the interviews a deliberate attempt has been made to obtain data that refer as far as possible to observed behaviour and actual events.

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CHAPTER VII

STATISTICAL ANALYSIS

The information collected has been transferred to computer cards and then to the magnetic tape of the computer Since the investigation has been in progress for several years various types of computer have been used. Most of the results presented here have been obtained with programmes for the D 21 Saab Earlier analyses were carried out using an IBM 2.

The methods of statistical analysis employed are conventional and will be found in any up-to-date standard work on statistics. (1 3 4 5)

X^2 has been the method most frequently used. Observed frequencies of a defined observation have been related to the frequency which a random distribution has been theoretically assumed to produce In practically every case the entire material has been used for each analysis Sometimes as a tentative test only extreme groups have been used, but they have generally been supplemented by a division of the entire group into two or three (fourfold and sixfold tables respectively)

In the variable analyses containing quantitative numerical magnitudes mean values standard deviations and mean errors have been calculated. The differences between mean values have been tested in ordinary t-tests

Median value differences between two samples (e g boys and girls) have been tested for significance by X^2 comparison of frequencies of deviation from the median in the aggregate sample the "median test

Correlation estimates ad modum Pearson have been used to elucidate the degree of correlation. The probability of the estimated coefficient of correlation not being random has been tested using the methods specified.

Certain comparisons have been made with the simple sign -test and the confidence limits have been obtained directly from Scientific Tables (2)

The three levels of significance used throughout are $p < 001$ (= highly significant) $p < 01$ (= significant) and $p < 05$ (= probably significant) Sometimes the value of the degree of significance between these three is indicated to show the proximity to the higher level of probability

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SUMMARIES OF THE REMAINING PREVIOUSLY PUBLISHED PAPERS

Breast feeding and weaning: some social psychological aspects

Differences with a statistical significance on at least the 2 % level were observed as follows:

1 boys were weaned later than girls
2. older mothers (26 years and over) continued breast feeding longer than younger mothers (< 26 years)
3 mothers in higher social classes continued breast feeding longer than mothers in lower social classes (Graffar I + II vs III vs IV + V)
4 better-educated mothers continued breast feeding longer on average than mothers with only compulsory elementary education
5 mothers who continued breast feeding for more than 6 months were on average possessed of greater self-confidence method and calm.

Weaning before six months was very seldom occasioned by the mother s resumption of gainful employment The commonest reason was that the supply of mother s milk failed without any demonstrable influence from external factors During the first months the mothers attitude to breast feeding while this was in progress was generally positive but this professedly positive attitude was of no predictive value regarding the duration of breast feeding

The sleep behaviour of children up to three years of age

Mean values and standard deviations are given for length of sleep at 6 9 12 18 24 and 36 months. There is no appreciable correlation between the total length of sleep per day and season or hours of sunshine. The correlation coefficient in a comparison of length of sleep at different ages was at most .49 No statistical relation could be established between length of sleep and a large number of tested variables including overcrowding and gainfully employed mothers

Different forms of wakefulness which occurred were analysed. These included resistance to bedtime preparation evening wakefulness and night waking Sleep disturbances were a recurrent characteristic of children s sleep behavior during annual periods For none of the periods did the occurrence of nightly waking fall below 23 % No connection could be established between night waking an environmental factors On the other hand the firstborn children showed a significant frequency of resistance to bedtime preparations Similarly the experience of separation from the family owing to a period in hospital or children s home or some other form of care in strange surroundings led to resistence to sleep by children aged between 2 and 3

The group of children who had been consistently bad sleepers for at least 2 years was compared with children who had slept without disturbances Of the variables tested only overcrowding and late weaning were related to this tendency to wakefulness Of all the methods employed for settling children in case of night waking the mothers claimed that the most effective under 18 months was to give them food while for children over 18 months the best solution was to let them get into the parents beds

Differences in infant feeding and elimination training in five European longitudinal samples (Hindley et al)

The ages for weaning from breast and bottle feeding and for the start of toilet training were compared in child samples from Brussles London Paris Stockholm and Zurich. Large discrepancies were found in all three respects

The median age when the last breast meal was discontinued varied from 0 9 months in the Brussles sample to 4 5 months in the Stockholm sample

The median age at wich bottle feeding ceased ranged from 13 3 months in the Zurich sample to 17 5 months in the London sample

In the case of the age at which continuous toilet training was started, the variation was from a median of 4 6 months in the London sample to 12 4 months in the Stockholm sample

The differences between the samples were considerably greater than those within each sample that were attributable to differences in social score

The differences in cultural patterns and in attitudes to methods of handling children were discussed.

Differences in age of walking in five European longitudinal samples (Hindley et al)

The study was designed to compare data on the ability to walk without support for children from the five longitudinal studies in which information had been collected concurrently and with the same technique The number of children in the individual samples ranged between 152 and 272. In all the samples the cumulative distribution of the age of first walking described a practically straight line between the 5th and the 95th percentile on a logarithmic scale indicating normality

The age of first walking did not differ by social group or by sex in any of the samples Significant differences were found, on the other hand, between the median ages for each of the five samples Conceivable causes of this were discussed, e g genetic factors feeding conditions and the way the parents cared for the child.

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CHAPTER IX

NON-NUTRITIONAL SUCKING IN AGES FROM INFANCY UP TO 8 YEARS OF AGE.

DEFINITION

The activity of sucking described and analysed in this essay comprises the sucking of fingers or a comforter without involving the assimilation of food.

MATERIAL AND METHOD

Data forming the basic material for studying the part of non-nutritional sucking has been taken from interview form VI items 11 12 and 13 for the ages of 1 - 6 months items 11 and 12 for the ages of 9 months - 5 years and in form V item 32 for the ages of 6 - 8 years

The habitual characteristics of sucking and the efforts of other persons to stop the habit have been estimated at every examination from the age of 1 month and up No occasionally" and definite habit are the degrees by which the group with a daily frequency are distinguished from the more occasional and from those without any extra sucking activity A child, who every night before falling asleep puts his thumb in his mouth has been noted as definite habit even if the activity mainly or solely is connected with this occasion. Data on the intensity of the habit are available at the ages of 1 - 6 months and 4 - 5 years The efforts of other persons to put an end to the occasional or the habitual behaviour have been graded into none mild, or intensive

Concerning the construction of the variables and the items forming part of the statistical tests of significance to illustrate the habit of sucking the reader is referred to the later parts of the presentation where etiological theories are tested (page 39) and the connection between the prolonged habit of thumbsucking and emotional symptoms is illustrated (page 45)

FREQUENCY

Result

The occurrence of the stated behaviour according to crossectional analyses made at different ages is illustrated in the frequency graphs fig 1

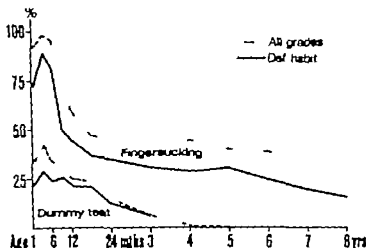


Fig 1 Incidence of finger/comforter-sucking at various ages Percentage distribution. Crossectional figures

Practically all children in the sample resorted to non-nutritional sucking during their infant year More than half of the girls and two-thirds of the boys had stopped sucking their fingers at the age of 18 months The frequency curve declined steeply during the latter part of the infant year This coincides with the periods when sucking is used less and less for feeding The teething period has started and the child receives a growing proportion of solid food

After this time and throughout the pre-school stage there is only a slow reduction in the number of fingersuckers Of the 78 children who at the age of 18 months had developed a definite habit of finger-sucking 80 % still resorted to some kind of fingersucking at the age of 6 The corresponding figure at the age of 8 was 61 %.

The 5-year-old fingersucker for example is more seldom a child who has relapsed into a previous habit In most cases the child had the habit all the time Only a quarter of the cases in the ages 3 - 5 was an irregular and periodical practicer of the habit

The frequency curve of comforter-sucking showed much the same form as that of fingersucking though at a lower level (fig 1) On the average the comforter-sucker abandoned this habit far earlier than the fingersucker At the age of 1 year 25 % of the children still used a comforter habitually while only a few percent still did so after the age of 4

Few children resort solely to comforter-sucking initially Contemporaneous fingersucking may ever be intensive but those who practiced both habits made up only 26 28 and 19 % at the ages of 1 3 and 6 months respectively The frequency of this contemporaneous sucking reached a peak between the ages of 3 - 6 months irrespective of intensity Later during the second half of the infant year there was a stronger reduction of thumbsucking than of comforter-sucking in addition to a general decline of sucking activity Even if the child after a time of contemporaneous comforter-sucking chose the thumb the fixation to the thumb generally lasted a shorter time than if he had resorted to thumbsucking only

For the intensive thumbsuckers at 3 months of age combined with habitual comforter-sucking the median age for the cessation of all sucking activity in question was 28 1 months The corresponding age for intensives without comforter-sucking was 62 5 months The difference according to the median test is significant at the 2 % level

Evidently it is not just a coincidence that only 2 out of the 59 children who used a comforter up to the age of 1 year came to belong to the group of fingersuckers practically throughout pre-school age Only 3 % of the habitual 5-year-old fingersuckers had used a comforter during their infant year; the others had started directly with fingersucking The probability of the difference being due to chance is very slight

Discussion

In this sample fingersucking comforter-sucking or a combination of the two are so frequent during the first part of the infant year that they cannot be described either as "bad habits" or as unusual ones. This frequency indicates a need of sucking either inherent or learned which is not sufficiently satisfied by nutritional sucking. Sucking activity reaches a peak during the first 6 months. After a steep decline before the age of 1 the frequency curve displays a quite different gentle slope during the following years. This could be interpreted as a sign of different sets of reasons during the infant year as compared with a later age. The frequency curve is in agreement with Benjamin's suggestions following experiments with monkeys that thumbsucking could begin for one set of reasons and be sustained for others (1). Evidently the non-nutritional sucking which occurs for example at the age of 3 months has a rather uncertain predictive value concerning sucking activity in the pre-school stage. However a habit of fingersucking which has been developed at the age of 1½ years is very difficult to get rid of. In most children it remains for several years. Finger sucking as a symptom is strikingly constant but the same is not as true of comforter-sucking. The cause of the difference can only be presumed. The simple fact that the thumb is more accessible than a comforter may guide development of the habit. Once established, the habit of comforter-sucking finds no replacement in fingersucking when it comes to an end.

S E X   D I F F E R E N C E S

Result and discussion

Finger-sucking is in this sample from the age of 12 months much more frequent with the girls than the boys In table 1 is seen the X^2-values for sex-differences in fingersucking

Table 1 Sex-differences in various ages

Chi square comparison p = probability level

Age	X^2	p
1 month	negligible	–
3 months		–
6		–
9		–
12	4 505	05
18	5 056	025
24	8 872	005
3 years	4 621	05
4	7 868	005
5	9 183	005
6	9 351	005
7	12.653	001
8	9 399	005

At every age level examined, from 1 year up to 8 the difference is statistically significant or probably significant which corresponds to the stability of the habit If the group of habitual comforter-suckers is combined with the group of habitual finger-suckers the sex difference at 12 months still shows that the girls resort to extra sucking more commonly than the boys (X^2 = 3 671) It is not clear whether this difference is real or illusory inherent or conditioned. Marjorie Honzik (11) who has studied the literature in this field and participated in one of the longitudi-

nal California studies points out that the information concerning sex differences is contradictory for one thing because of the combination of ages in the material examined The distinct sex difference observed by her in children of pre-school age is according to her a real sex difference concerning sensibility and satisfaction of tactile stimulations

Naturally a child s early sucking activity is mainly connected with nutritional sucking For a whole lot of children evidently this sucking is enough as a source of satisfaction at least at the time during the second part of their first year when the need is decreasing If all kinds of sucking activity at the age of 12 months including nutritional sucking are combined in the previously mentioned test on different sucking behaviour in boys and girls the statistical sex difference disappears The total number of children with some kind of sucking either conditioned by feeding or occurring as extra sucking of fingers or a comforter is divided rather evenly between the sexes (χ^2 = 0 139) Neither is the sex difference significant if the same calculation is made at the age of 2 on the basis of information on conditions between the ages of 1½ and 2 (χ^2 = 2 173) Later on however when nutritional sucking has ceased, the girls greater frequency becomes manifest

It has been pointed out (13) that the boys in this sample were breastfed longer and also bottlefed longer than the girls If a certain period of time is of importance for learning or developing the habit for example at the end of the first year when nutritional sucking is decreasing the girls more than the boys run the risk of being fixed to the need of extra sucking According to the reasoning presented here the sex difference observed might well be due to differences in the way the practice of feeding has developed.

ETIOLOGICAL VIEWPOINTS

INTRODUCTION

The sucking activity of an infant is mainly connected with the satisfaction of its nutritional needs Therefore the relation of extra sucking to the feedinghabits of the children has a strong bearing on etiological considerations This applies to the origin of the habit of fingersucking but it hardly considers the fact that the child sustains the habit After infancy the comforting function seems to dominate Some children find satisfaction in fingersucking or in comforter-sucking when going to sleep when worried or when they just want to increase their well-being

All the issues introduced in this section touch on the two contradictory hypotheses mentioned in the introduction, the psycho-analytic one and the one which claims extra sucking to be a product of learning The information from the mothers at the longitudinal follow-up should be fairly reliable since the intervals between examinations have been rather short It is not probable that the child s changing behaviour at feeding can have made the mother remember or interpret things erroneously which otherwise might be the case

Material and method

Finger/comforter-suckers with a habit of at least 3 years have been compared with the rest of the children in the sample with respect to: the kind of feeding different times for weaning from the breast and for the cessation of all nutritional sucking the degree of satisfaction at a meal crying the length of a meal and anxiety before a meal Finally the intensity of habitual extra sucking in the infant at no more than six months has also been used to illustrate the prediction of the maintenance of this habit

The items concerning feeding which have served as a basis for the comparison have been taken from form V Concerning the issues connected with items 34 - 41 there is information from every examination about the number of breastmeals and bottlemeals a day Items 34 and 38 deal with the time of weaning from the breast or the bottle Sucking is involved in both kinds of feeding and since the method of feeding does not seem to influence the frequency of fingersuckers (see below under Result) the more meaningful term nutritional suckers has been used to cover both. The age at which nutritional sucking ceased has been established.

Item 32: 7 8 9 gives information about the observations and complaints related by the mothers concerning meals The child may not have been satisfied at the meal it may not have wanted to stop eating or it may have eaten too fast; in other words the observations concern something remarkable at the end of a meal

The average time of sucking at meals varies from child to child. Even if the mothers information about how long a meal lasts is approximate there must be a considerable difference between the extremes The grading in minutes is given in item 52.

The child s anxiety before a meal has been estimated by the mother in stating the number of minutes that the child usually screams before it is given the breast or the bottle This is naturally a discretionary judgment which has certain limits concerning exactness. Still the information ought to indicate different degrees of frustration between the children who are left to scream (> 10 minutes) and those who keep waiting happily or with a slight degree of irritation (item 63:0 7 8 9)

Information about the intensity of the fingersucking habit during the first 6 months is to be had in form VI, item 11:0 - 5)

Result

The results from the significance tests are compiled in table 2 The feeding situations used in the comparison between the 3 year old habitual suckers and the other children are listed as variable headings

Table 2. Feeding conditions of finger/comforter-suckers (> 3 years duration) versus those of non-suckers

s	χ^2	p	Number of children in group
bottlefed (from before 2 mths) /others	negligible	n.s	n = 209
( ) /breastfed >6 mths (extremes)			n = 142
d from the breast before/after 4 mths ♀			n = 88
♂			n = 121
6 ♀			n = 88
♂			n = 121
between 1 – 3 vs others ♀			n = 88
♂			n = 121
" 2 – 4 vs others ♀			n = 88
♂			n = 121
2 – 5 vs others ♀			n = 88
♂			n = 121
from nutritional sucking			
before/after 9 mths	6 570	02	n = 209
/ 12	4.169	05	n = 209
fied at meals at 1 and 3 mths/others	7 187	01	n = 209
1 3 and 6 mths/others	5 642	02	n = 209
ion of sucking at a meal at 3 mths long suckers/short suckers	4 191	05	n = 91
g long before meals at 3 mths as well as 6 mths/others	negligible	n.s	n = 209

Ad 1. Bottle- and breastfeeding Finger/comforter-suckers whose habit lasted at least 3 years did not differ from other children concerning bottle- or breastfeeding during the infant years Those who had been fed mainly with a bottle became fingersuckers to the same degree as the others Nor was there any obvious difference between bottle-children and late-weaned breast-children i e those who had been given breast-meals up to 6 months or longer Hanna (9) has newly reported much the same

Ad 2. Weaning from breast Weaning from the breast with the loss of an assumed better psychological climate has been held to be of great importance as a cause of fingersucking (12) The test scores for groups weaned at different times do not confirm the idea that the cessation of breastfeeding as such influences the existence and persistence of fingersucking Nor is the assumption reasonable that a certain period of weaning (for example between 2 and 4 months) involves a greater risk of adopting a certain behaviour than other periods of weaning (23)

Ad 3. Weaning from nutritional sucking For a about one quarter (54 children) of the more than 200 children nutritional sucking ceased before the age of 9 months Among these children finger/comforter-sucking up to at least 3 years occurred comparatively more frequently than among those who had been weaned after 9 months The statistical test is significant at the 2 % level When the limit for the cessation of nutritional sucking is set at the age of 12 months the test gives a response at the 5 % level The chances of satisfying a well-established need for sucking are naturally greater during a longer period of nutritional sucking According to the learning theory however (see below) a longer period of sucking would also increase the chances of fixating the need It i therefore noteworthy that out of the 21 children of both sexes who between the ages of 2 - 3 years still received one or more sucking-meals a day (one was still breastfed) only 3 belonged to the group of comforter-thumbsuckers with at least 3 years of habitual sucking (X^2 = 6 012 p = 02)

Ad 4. Satisfaction at meals At the examinations during the first 6 months (at 1 3 and 6 months) the mothers stated that 36 children

were more or less unsatisfied when they had stopped eating 20 of these children later belonged to the group of finger/comforter-suckers The probability of a sucking habit developing seems to be significantly greater if the child has displayed symptoms of discontent or dissatisfaction at the end of a meal than if it has been classified as satisfied.

When only the conditions at 1 and 3 months are taken into consideration, the difference becomes even more marked (X^2 - 7 187 p = 01)

Ad 5. The length of a meal The graph showing the average duration of a meal with children of 3 months of age suggest that this function is normally distributed The 20 % short-suckers have been compared with the 27 % long-suckers Those in the second group resort less to prolonged extra sucking of at least 3 years (p = 05)

Ad 6. Crying before meals Incitements to extra sucking should be more frequent in the crying group than in the patient one The children who have been noted as crying more at the ages of 3 and 6 months stop their thumb/comforter-sucking before the age of 3 years just as often as the others Nor is there any apparent connection between prolonged crying while waiting for food and intense thumb-sucking at the age of 3 months (X^2 = 0 556 p = no signif)

Early intensity of the habit About as large a proportion of boys as girls have been noted to be intense thumbsuckers This applies to the ages of 1 3 and 6 months and the number of intense suckers increases significantly with both sexes (X^2 = 16 68) between 1 and 3 months Between 3 and 6 months there is only a slight increase the frequency amounting to 48 % of the girls as well as of the boys at 6 months

A significance test concerning the intensity at an early age and a later habitual sucking has been performed with the girls in one group and the boys in another The girls who were judged by their mothers to be intense thumb- or comforter-suckers at either 1 3 or 6 months featured no more frequently than others in the group who were still habitual suckers at the age of 3 years As regards

the boys there is a probable significance that those who had been intensive suckers at 3 and 6 months respectively continued to suck at least up to the age of 3 years while most of the non-intensive ones had stopped. The intensity at one month of age did not make any difference to the frequency of extra sucking at the age of 3 years

Discussion

Concerning the discussion of the accumulated results of relations to feeding the reader is referred to the general discussion on page 54

PROLONGED FINGERSUCKING (> 5 YEARS) IN RELATION TO EMOTIONAL SYMPTOMS

INTRODUCTION

The habit of fingersucking slowly disappears during pre-school age and the first years of school and it may be asked why this infantile sucking manifestation persists so much longer in certain children than in others Even though, as illustrated the continuation of sucking as an expression of a need for comfort may have a possible influence Indications of an increased need of comfort will be examined with the following questions: Does the group of children with prolonged fingersucking display any stress factors which may distinguish this group from the non-suckers? Have the fingersuckers any accumulated symptoms of psychological imbalance during the pre-school stage which cannot be found in others and which would indicate a connection with an environmental influence?

Method

To illustrate these questions the group of 62 children (38 ♀ + 27 ♂) who sucked their fingers up to at least 5 years of age has been tested against another group in the sample with respect to certain psychological psychosomatic and social variables according to Table 3

Children with appetite troubles are those who have been said to have a bad or not-so-good appetite at (a) half of the examinations and (b) more than half of the examinations from 1 to 5 years of age (Ta 36: 6 7)

The variable "Night disturbances refers to (a) poor sleepers up to 3 years old (groups IV and V according to the definition in the essay on sleep behaviour in Acta paed. (15) and (b) children who have often, at 4 and 5 years of age woken up in a state of emotional anxiety

The variable Stuttering" refers to all kinds of nonfluent speech disturbances The answers to the question "Does he stutter at all? have been divided into "no occasionally" and often The degree of speech disturbance has been determined from the child s condition at two of the three examinations between 3 and 5 years of age In a 6-column table a comparison has been made between children with and children without fingersucking

Opinions about sensitivity and liveliness in the children have been divided into three degrees: sensitive - medium - stable and lively - medium - quiet respectively At the ages of 3 or 4 there is no sex difference in this behaviour The children who have been conside-

red quiet amount to only a little more than 10 % There is no obvious connection with fingersucking

The occurrence of destructiveness in children divided into never occasionally" and definite habit is a definitely sex-divided characteristic at 3 as well as 4 years of age (see ch. XV) The boys predominate in a statistical comparison on at least the 1 % level Special calculations have therefore for boys and for girls been made with respect to the connection with fingersucking The result showed no significant connection with either group The figure in the table refers to both sexes

In the correlation to the mother s employment the children of mothers who have been employed at all during the child s first 3 years have been compared with regard to fingersucking to those whose mothers have not been employed during this time

Result

The results of the significance test are summarized in table 3

Discussion

As the table shows of all tested variables only the mother s employment gives a result in the statistical test The children whose mothers are housewives are significantly more common among the fingersuckers than the children of employed mothers Since fingersucking is partly an evening habit not even a full-time employed mother could help observing it The children of employed mothers generally have a more extrovert life and more contacts with others Fingersucking has been regarded as a simple reaction to boredom tiredness disappointment and punishment i.e the habit is used as consolation. Those who become fixed to this habit of satisfying themselves early or often continue to do so for years There is nothing however which indicates that the fingersuckers up to the tested age have a stronger need for consolation in comparison with others and the fingersucking consequently should be one symptom among others of a general emotional lability or of a disturbed personality development For most children the pre-school age is filled with troubles There are many ways of trying to escape troubles and find satisfaction. Some children seek their satisfaction in fingersucking others elsewhere Those who have come to like the sensuous oral sensations or have grown accustomed to a certain behaviour find it difficult to give it up Fingersuckers are no more than others characterized by stress-symptoms or by any

Table 3 Psychological and social variables in fingersuckers whose habit lasted at least 5 years in relation to others (n = 204)

ble	Interview form Nr item and dig	χ^2	p
ite troubles 1-5 years			
half of the examinations	V: 31: 6 7	negligible	n.s.
>	V: 31: 6 7		
les with weaning from tional smoking	V: 57-58: 7 8		
disturbances:			
tance at bed-time at 3 years	VI: 55: 8 9		
waking 9 months - 3 years	VI: 61 o 63-66		
with anxiety 4 - 5 years	VI: 61:7-9 o 62:4 5		
h disturbances:			
ering 3 - 5 years	V: 67: 8 9		
(of all kinds) at 4 or 5 years	VI: 20: 4-9		
iting (of all degrees) 2-5 years	VI: 13: 4-9		
tivity at 3 years	VII: 76: 7-9		
iness	VIII: 75: 6-9		
motiveness at 3 years	VII: 58: 8 9		
ers or brothers before the age of 3	O: 17		
l gr Graffar modif at 3 years	O:76: 1-5 (longitudinal)		
other s education when the l is 3	O:80: 1-5	4 895 (2df)	
wife / employed during the l s first 3 years	O:20: 1-4	7 106	01

other kinds of behaviour that characterize children with difficulties in adjusting themselves or children with psychological problems

SEQUELAE OF FINGERSUCKING

FINGERSUCKING - MALOCCLUSION

Introduction

Those who have studied fingersucking and its consequences are now agreed that attention should be focussed on its effect on the jaws and teeth. In the 1920 s malocclusion was a bogey which made many parents dentists and pediatricians heavily oppose the habit of fingersucking. They tried to cope with the problem, using various ingenious means of compulsion. The reaction which followed referred among other things to longitudinal studies of anomalies of the bite which gave a less rigid picture of the causes (5 4) Malocclusions have many causes only one of which is finger/comforter-sucking Moreover even an habitual thumbsucker can have an adequate occlusion (17) To find out to what extent the children in this sample have developed malocclusions as a consequence of finger/comforter-sucking contact was established with the Institute of Orthodontics at the Royal Dental College in Copenhagen, where there is an intimate acquaintance with these problems. Studies have been made on the occurrence of malocclusions in several races with different sucking habits or no such habits at all (3 4 10) Investigations have also been made into the functions of the tongue and the lips in children with sucking habits Thanks to their courtesy 136 of the children in the sample (those who could be present on this occasion) at ages between 9 and 12 years have been examined at various stages of eruption of their second dentition.

Result

Briefly it can be said that in the groups with sucking habits (prolonged fingersucking and comforter-sucking) 13 % more than in the groups with minimal or no sucking were registered as having symptoms of malocclusion. The difference is not statistically significant (χ^2 = 2.498) but even considering special anomalies it points consistently in the same expected direction. For example there was an increased occurrence of extreme maxillary overjet and of open bite in the group of finger/comforter-suckers and furthermore a higher frequency of deep bite among early comforter-suckers Distal molar

occlusion was most common among the fingersuckers while mesial molar occlusion occurred more often among the comforter-suckers The groups are too small to give a reliable statistical result. It should be noted that 6 of the children with prolonged thumbsucking and 2 of the 9 most persistent comforter-suckers were free from symptoms

Discussion

An absence of symptoms is thus compatible with habitual extra sucking Certain occlusal anomalies are furthermore conditioned by development and relatively common during growth (3 9) Renewed examination of the bite after puberty in the material as a whole is expected to give information on the degree to which the physiological tendency to normalization is made more difficult by prolonged sucking

FINGERSUCKING - ARTICULATION TROUBLES

Introduction

Articulation defects are possible consequences which have rarely been discussed (27) The pronunciation of consonants might be sensitive to deviations in the positions of the teeth and jaws of the tongue and the lips The relative frequency in the groups with different sucking activities during the period of speech development ought to indicate to what extent these divergences are reflected in articulation troubles

Method

Such a judgment has been applied in the present material to children at 4 and 5 years of age This age was chosen with regard to ordinary speech development which is considered to have reached maturity in enunciation at this time (see essay on speech development) The articulation defects have been exemplified by the mothers. The information is derived from form V: item 68: 1 3 5 It is mainly concerned with lisping and other difficulties with the s sounds (26 cases) and the r sound (8 cases) There are also some children who find it difficult to pronounce v f t and k. A combination of defects in the pronunciation of consonants is not unusual No detailed phoniatric analysis of the defects in articulation has been included in the study

Result

Table 4 shows a relatively higher frequency of pronunciation defects in children with prolonged fingersucking than in others The difference between the groups is statistically significant both concerning articulation defects in a wider sense including lisping (p = 01) and concerning lisping only (p = 025) These articulation defects at 4 or 5 years of age which have been observed by the mothers tend to disappear when the child reaches school age In 8 out of 20 children who had dyslaly as well as prolonged sucking at 4 and 5 years of age a noticeable articulation defect remained during their first year of school Nearly all the 20 children were still thumbsuckers when they started school. 5 children remained out of the other 20 with stated pronunciation defects At 8 years of age there is still a tendency though not statistically significant for some slight discrepancies in pronunciation to be more common among habitual fingersuckers than among the other children.

Table 4 Faulty articulation and lisping among fingersuckers and others

	n	Articulation errors at 4 or 5 (except lisping)	Lisping at 4 or 5 yrs
Fingersucking 5 years	65	10	10
Others	139	12	8
Total	204	22	18

PARENTAL REACTION

Introduction

Observations in connection with forced weaning from fingersucking have raised the question of whether disturbances in the children s psychological balance are a consequence of such weaning Bedtime troubles night waking increased screaming increased obstinacy bed-wetting and general symptoms of discomfort have been reported (15) The question related here is to which extent parental reactions on fingersucking nowadays do exist

Method

A systematic registration has been made of the parents measures against extra sucking of this kind from 1 up to 5 years of age but unfortunately not beyond that The attempts to stop the habit mostly consist in telling the child to stop and promising him something extra if and when he does. The measures which have been classified as intensive are: consistent threats with a frightening touch, for example that hands and nails will be disfigured that the thumb may fall off that "bad germs will get into the stomach.

Result

Mothers attitudes towards the sucking habits of children are nowadays characterized by tolerance The attempts to stop fingersucking or comforter-sucking up to the age of 3 are mostly very mild. Corporal punishment has been reported only in one case where the father hits the child and the grandmother threatens to backbind him, while the brothers and sisters insult him.

The worries that sucking may bring about difficulties increase if the habit persists to a higher age "Intense attempts at weaning have been made on a few children at the ages of 4 and 5 without any immediate results The 4 children subjected to what have been noted as intense attempts were still fingersuckers at the age of 7 and 3 of them were still habitual suckers at the age of 10 They include the maltreated child mentioned above

Equally bad results are yielded by a comparison between the fingersuckers aged 4 and 5 years upon whom only mild attempts have been

Table 5 Measures against fingersucking at different ages calculated on the number of children with fingersucking (occasionally + definite habit)

Age in months	Mild attempts %	Intense attempts %
12	1 6	
18	3 2	
24	9 7	
36	20	1
48	25	
60	32 6	5

made to stop the habit and a similar group which has been left alone The two groups have much the same percentage of fingersuckers at the age of 8

The mother s education has not been of any significant importance when deciding whether or not measures should be taken (χ^2 = 1 247)

Discussion

Evidently information about the ineffectiveness of using coercive measures has reached mothers of different levels of education The vast arsenal of mechanical aids for stopping infant thumbsucking which was described 20 years ago (15) is no longer to be found.

GENERAL DISCUSSION

Contradictory facts concerning the etiology of the origin of thumbsucking and its persistence can be had from the literature Compared with all the reflections about its consequences there are remarkably few experimental or analytical facts to support any hypotheses about its origin. According to psychoanalytic theory thumbsucking is an autoerotic activity and the lips are an erogenic zone (7 12) Sucking in connection with eating and the abatement of hunger gives a satisfaction which is transformed to be associated with the act of sucking According to the theory of learning which has grown stronger in the last few years (1) the congenital suckingreflex can be weakened to different degrees depending on the intensity and persistence with which it is exercised Prolonged thumbsucking is regarded as a product of learning which has been conditioned by its original pleasant association with food and care (20 28) Consequently there is an intensification of the normal sucking reflex through repetition unconnected with feeding If this intensification is stopped by the infant s wearing mittens every day at special hours during the first months as in Benjamin s study (2) the result is that fingersucking later occurs much less frequently among these infants than among the controls According to this hypothesis the hours when fingersucking is to be made impossible are when the rooting and placing reflexes are maximal This occurs when the child is hungry or when it is put to bed in such positions that the hands can easily touch the cheeks and mouth. It has been shown (6 8) in 1948 that some children who were fed with a cup instead of a bottle or the breast never developed sucking reflexes of any noteworthy intensity Under these circumstances it seems strange that no statistical connection between the anxiety of hunger (crying) and thumbsucking could be established in this study There is better correspondence with the statements by Korner et al (16) in 1968 after direct observations of bottlefed new-born babies that only mouthing (different movements of the mouth) was significantly hunger-related while fingersucking a hand-to-face and a hand-to-mouth activity lacked any observable connections At this early age however a deliberate movement of the hands towards the mouth is physiologically impossible in which case the touch would be conditioned by the situation.

According to the theory of learning it is also difficult to explain why children with both an intense fingersucking and an habitual comforter-sucking stop with either or both at a considerably younger age than those *who have resorted to intense fingersucking* only The stronger use of sucking ought to give the opposite result It is also difficult to explain why children who suck longer at meals become fingersuckers less often than those who suck for a shorter time Roberts (22) has reported findings in the same direction. What is easier to explain however is that the children who have been classified as being satisfied at meals do not need any extra sucking.

The stimulus limen to induce a sucking reflex is lowered at hunger Everything that touches the area around the mouth and cheeks seems to make the child move its mouth and turn its head towards the object A touch on the lips induces sucking movements Evidently this *series* of mutually related reflexes has a practical *purpose* In the light of these facts it is therefore not at all sensational nor is it *difficult to interpret* that *practically all children in this* sample (all nutritional suckers) have been noted as resorting to some kind of extra sucking at 3 months of age From a preventive point of view it is more important to know why the fingersucking in a larger group of children persists beyond the age when sucking activity is normally reduced. A longitudinal study is in a better position to illustrate this than other studies but even so it has not been possible to present a convincing comprehensive explanation.

One thing is evident however that the thumbsucking child of preschool age may have or lack emotional stress symptoms to the same degree as his non-thumbsucking peers It should also be noted that Tryon (29) in his test (The Childrens Manifest Anxiety Scale) has not been able to show any differences in symptoms of anxiety Observations and reports that fingersucking is indicative of emotional disturbances (12) have probably been based on individual cases. It is also possible that a part may be played by the children s inherent differences of temperament differences in their sensibility towards stimulation of the lips or differences in their demands for satisfaction of needs The *observation* that those who are inten-

as suckers from the very beginning (this applies only to boys) are likely to develop prolonged sucking can just as well be interpreted this way as being a sign of learning

As a basis for an explanation it is not enough to regard thumbsucking as a product of learning. The weaknesses of the theory become evident when the development and disappearance of the habit in a group of children is observed in relation to feeding conditions Only a small number of the children with real prolonged thumbsucking come from the group who were both thumbsuckers and comforter-suckers in infancy although one might suppose that these children would run a greater risk of developing a need for sucking

SUMMARY

The origin, frequency and gradual decrease of the habit of fingersucking during the first 8 years have been studied in 212 children involved in a longitudinal study of growth. This extra sucking of the whole group stops at a median age of 12 9 months Comfortersucking in combination with intense fingersucking at 3 months results in a significantly lower median age (28 1 months) than does fingersucking alone (62 5 months) A fingersucking established at the end of the infant year decreases very slowly

A sex difference with a significant dominance of girls becomes evident on each level from 1 to 8 years It is possible however that the time of cessation of nutritional sucking which is relatively late for the boys in this sample may determine the indicated sex difference

Significance tests were made of the correlation between fingersucking and the mode of feeding Breast- or bottle-feeding makes no difference but the time of cessation of nutritional sucking the duration of the sucking meal and the satisfaction at this meal are inversely correlated to prolonged thumbsucking in a way which cannot be coincidental

Eleven psychological and four social variables have been significance-tested in their relations to the prolonged sucking habit and are illustrated in tabular form. It has not been possible to prove that emotional stress symptoms distinguish long-term thumbsuckers from others Housewifes have more fingersuckers than mothers gainfully employed during early ages of the children.

The effects of habitual fingersucking with respect to malocclusion and articulation defects have been studied. Slight discrepancies in pronunciation occur significantly more often in 4 - 5 year old thumbsuckers than in others In the group with sucking habits 13 % more children had symptoms of malocclusion than in the group with minimal or no sucking The difference is not statistically significant but even concerning special malocclusions it always pointed in the same

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S U M M A R Y

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CHAPTER X

N A I L B I T I N G

N A I L B I T I N G

INTRODUCTION

Kanner asserts in his textbook (5) that nailbiting is an expression of emotional tension and that it is the most widespread of habitual manipulations of the body among children. Yet curiously enough, we also read that this widespread habit was regarded at the turn of the century as an exquisite psychopatic symptom or as a sign of degeneration (ibid.) Nowadays nailbiting in itself is never the occasion of a clinical examination. Insofar as it is accompanied by other nervous traits and symptoms of maladjustment it has come to figure as a sub-symptom in child psychopathology But experience gives us every reason to suppose that the phenomenon is an everyday problem of childhood rather than an indicator of any seriously disturbed psychic relations The frequency and persistence of the symptom together with its covariation, if any with other emotional symptom variables have however been considered worth examining using data from the 212 children of the longitudinal study

Method

The incidence and intensity of nailbiting have been noted in interviews from 2 - 5 years (form VI: 13: dig 0 - 9) and from 6 - 8 years (questionnaire V: 33: dig 0 - 4) Data collected during the first of these periods have been concerned with the habitual nature of nailbiting (occasionally phenomenon or definitive habit) and the intensity of efforts made to put a stop to the habit

The information provided by the mother during the second period has unfortunately been solely concerned with frequency (several times daily often or daily sometimes seldom or not at all) The reaction of the child s environment to its nailbiting has not been described at this later age period.

RESULTS

Frequency

Fig 1 show the frequency of nailbiting expressed in cross-sectional figures between the ages of 2 - 8 years Since the graduations of the habit were given different names before and after 6 years comparisons for the entire observation period should relate to all degrees

of intensity taken together It will be seen that sporadic nail-biting at least becomes more common as children grow older

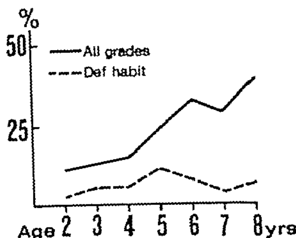


Fig 1 Incidence of nailbiting at various ages Percentage distribution. Cross-sectional figures

But the intensity varies If we only include those exhibiting the symptom daily nailbiting occurs in approximately 5 % when the children start school while approximately 15 % are occasional nail-biters. The rest up to nearly 40 % is seldom nailbiting

Sex differences

The symptom was consistently more common among girls than boys in this sample at every interview between 2 and 8 years At 5 and 6 years the tendency is so pronounced that a statistical significance of 01 and 05 respectively can be established.

Persistence of the symptom

Fig 2 shows the proportion of the sample who after first exhibiting the symptom at one age or another continued to do so to a greater or lesser degree at subsequent interviews Children reported as occasional nailbiters have here been taken together with those biting their nails daily The continuous curves which are superimposed on the cross-sectional frequencies (bars) represent children noted for nailbiting at every interview in the pure sample" The dashed curves show how frequently the symptom has recurred.

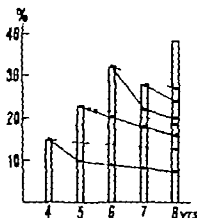


Fig 2 Persistence of nailbiting (all grades) 4 - 8 years of age

——— = persistent symptom at each investigation (pure sample)

- - - - = recurrent symptom at 8 years of age

Bars = frequency in cross-sectional pure sample at various ages

The most frequent grades also vary in intensity from one interview to another Fig 3 (the left diagram) shows how children noted for a definite habit at 4 years had changed one year later The right diagram in the same fig shows corresponding changes in daily nailbiters between 6 and 8 years

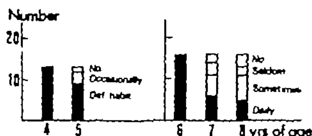


Fig 3. Changes in "definite habit" between 4 and 5 years of age and in "daily nailbiting" between 6 and 8 years of age

DISCUSSION

As can be seen from fig 1 the frequency figures differ considerably according to the graduation of symptom frequency on which the incidence of nailbiting is estimated Consequently there is little point in comparing frequencies with other cross-sectional investigations which do not generally have a similar division by grades of intensity Gedda (2) reports (1948) that he observed nailbiting in 7 % of children starting school (7 years) Jonsson and Kälvesten (4) found an approximate figure of 20 % in boys ages 7 - 16 years divided into a more or less equal number of moderately severe and slight forms Wechsler (7) who observed over 3 000 schoolchildren put the frequency of nailbiters at 56 %

Figures 2 and 3 show that nailbiting is a changeable symptom regardless of the degree of intensity noted at a particular interview The curves which denote the degree of permanence of the symptom, also indicate how once it has appeared a symptom can recur after a lapse of several years Thus nailbiting between 4 and 8 years is a symptom which varies in intensity in one and the same individual with longer or shorter periods when the symptom is either absent or only occurs to a negligible degree However if a child has chosen this mode of reaction at 4 - 5 years it is very likely to appear at subsequent stages of the observation period described here Children biting their nails at 6 7 or 8 years have had the same oral behaviour previously far more often than those who were not nailbiters at these ages

COVARIATION WITH OTHER VARIABLES

INTRODUCTION

The following hypotheses have been tested:

1) children who have stopped thumbsucking at 2 years or later have accordingly begun nailbiting

2) there is a tendency to covariation between temper tantrums and nailbiting

3) children noted for exceptional defiance symptoms bite their nails more than others

4) children with prolonged speech disturbances (recurrent proneness to stammering) or nervous twitches (tic symptom) are at the same time nailbiters to a notable extent

5) children with other forms of biting during early childhood will be nailbiters more than others

6) school start is related to deterioration of nailbiting

Method

Although nailbiting appears more or less periodically in the children in this sample one can distinguish a group of children in whom the habit persists year after year A group of 22 children (11 ♂ + 11 ♀) have been noted for the symptom at 5 or more of the 7 annual interviews between 2 and 8 years This group has been compared with the other children in certain respects

This group of persistent nailbiters has been used in certain of the above comparisons above all when testing covariations with other more permanent symptoms The other variables which have been employed are presented in the account of results

RESULTS

Relation to thumbsucking

Nailbiting is sometimes claimed to be a substitute for thumbsucking when the latter ceases The results derived from this sample do not indicate any probability whatsoever for such a connection The estimate has been made as follows: If the first report of the child nailbiting has been received in the same year as it stopped thumbsucking or the year after a connection has been assumed possible

Of the 106 children reported as nailbiting regardless of the degree of intensity at some point between 2 and 8 years there were only 12 whose abandonment of thumbsucking showed any conceivable chronological relation to the commencement of nailbiting. This proportion is within the limits of chance Fingersucking and nailbiting are not mutually exclusive Nailbiting can begin while a child is still fingersucking Nailbiters are not more predominant among those who stopped fingersucking before 5 years than among those who still suck their fingers (X^2 = 0.906 n.s)

Relation to temper tantrums

In order to test whether children particularly noted for temper tantrums were notably in evidence among the group of persistent nailbiters those whose mothers had described them at 2 of 3 interviews between 6 - 8 years as particularly temperamental (V:62: dig 3 4) were compared with the others The result was a random distribution (X^2 = 0 574)

Another test was also made concerning a possible covariation of temper tantrums and nailbiting Children noted for daily temper tantrums at 4 and 5 years (questionnaire VII: 54: 7-9) were tested for the occurrence of nailbiting during the three immediately succeeding years (between 6 - 8 years) The incidence was no more than coincidental The majority of the children included in the temper tantrums group had developed a more restrained disposition at this period between 6 and 8 years There was no notable increase in the frequency of nailbiting

Relation to defiance

Children considered particularly defiant by their mothers between the ages of 6 and 8 years (V: 50: 3,4) have been investigated regarding the incidence of nailbiting in the same way as those noted for temper tantrums Those considered most difficult at 2 of 3 interviews between 6 and 8 years (classified as often or always defiant when corrected) were compared with the rest The particularly defiant children included more members of the group of per-

sistent nailbiters than can be attributed to chance ($\chi^2 = 4.587$ p = 05)

Relation to stammering tendency or to tics

No such relation can be established. The variables employed for comparing covariation are enumerated in the essays on speech disturbances (page 142) and tics (page 207)

DISCUSSION

Temper tantrums are a typical age-related symptom. As they grow older children generally seem able to channel their tempestuous feelings over disappointments into more socially acceptable forms than bodily expression. Presumably those around the child show less disapproval of nailbiting than of the child lying on the floor and thrashing with its feet If the changes of temperament occuring between 6 and 8 years are an expression of self-control it is clear that nailbiting does not serve as a vicarious outlet for the emotions to any significant extent

The relation to defiance sheds an interesting light on the theory that nailbiting is a symptom connected with inhibited aggression directed against the child s own body The covariation is only probably significant Other causes appear to be involved. The situations in which a child or adult bites his nails are not as a rule consciously related to defiance or aggression but are more often than not described as a means of releasing emotional tension (1) The reasons for this tension can vary considerably and bear no apparent relation to an aggressive frame of mind. The influence giving rise to a symptom and converting it into a habit may be forgotten and the release which the habit provides may then be used for other reasons and purposes The analogy with the thumbsucking habit is by no means far-fetched. Probably it arises for one reason and then remains to be used in other contexts Nailbiting can be regarded as a functional automation, one of the original causes of which may lie in inhibited aggression.

Relation to other forms of biting

All prominent biting habits have been noted up to the age of 5 years These habits are for the most part an obviously aggressive symptom, but they also occur to a minor extent as expressions of play happiness and satisfaction.

The children noted for biting their siblings playmates or parents at various occasions or as a bad habit at 1½ - 5 years amounted to 83 = 41 % (30 ♀ + 53 ♂) The sex difference is not statistically significant At 3 years the figures for biting are 22 %, at 4 years 15 % and at 5 years 7 %

The covariation between nailbiting both of a temporary and a more persistent nature and biting of this kind in children between 1½ and 5 years has been tested (χ^2 = 0.443) Thus it does not occur in the same individuals more than one might expect from coincidence

DISCUSSION

The aggressive component in biting becomes more prominent with increasing age: at least this behaviour is interpreted as unfriendly by those who fall victim to it Whatever the frame of mind that prompts it be it playfulness aggression or defence biting produces a pain reaction which can easily elicit an aggressive response There are examples of siblings or playmates biting each other Generally however it is the adult (= the mother) who intervenes to punish, first by reproof or sending the child to bed or if the behaviour continues by corporal punishment Half the boys and a third of the girls biting in this way had immediately been administered corporal punishment Preventive or diversionary measures are reported less often. There is a striking difference between this reaction and the milder response to nailbiting (see page 70)

Assuming that nailbiting is an aggressive symptom (directed against the child s own body) one might expect theoretically speaking to find a demonstrable relation between aggressive biting and nailbi-

ting Nailbiting rises in frequency at the same time as aggressive biting declines as a result of development or of the pressure exerted by those around the child. The extroverted act of aggression is then forced into other channels in order that the child can attain the acceptance it seeks Nailbiting might be interpreted as a reserve channel of this kind for venting emotions of an aggressive natur The present investigation does not provide any statistical evidence for this assumption

Nailbiting seems to appear irregularly equally often or equally seldom in children who have or have not displayed a striking tendency to biting at 1½ - 5 years instead of occurring more frequently in the former category Although in individual cases nailbiting appears to be accentuated by conflicts between parents and children, the opposition displayed by parents to the habit is only one of many everyday situations capable of generating disappointment and emotional tension. Thus any relation is easily concealed. The evaluation of the personality tests may possibly provide a better basis for assumptions and reflections concerning the relation between aggression and nailbiting

Relation to school start

The diffuse tension which a child can experience when confronted by the strains of the first year at school have been regarded as a possible cause of nailbiting The frequency of the habit rises during the first years at school so that one is led to suspect a certain relation. If the symptom has appeared for the first time or become more regular i.e if a deterioration has occurred by the first interview after the child started school at 7 or 8 years the presumed relationship has been assumed probable If nailbiting previously established has disappeared or become less frequent this has been noted as an improvement Against this background the changes in connection with starting school noted for the 196 for whom adequate data were obtainable are as follows: deterioration 28 improvement 15 no change 153

According to the sign test the difference in number between the 43 children whose behaviour changed in one or the other direction is

just inside the 5 % confidence limit (see Documenta Geigy Scientific Tables p 105) In other words the only difference which can be established in this material is one which, notwithstanding its size may be coincidental

Children in the sample who were investigated within six months of starting school showed 14 deteriorations, 12 improvements and 88 no-changes with regard to nailbiting. Thus no definite rise in frequency can be observed in connection with this first period at school

PARENTAL REACTIONS TO NAILBITING AT 2 - 5 YEARS

Generally (= 80 %) mothers react to the behaviour even when the children are small and try by various means to cure them of it But the reaction is not particularly strong Of the total number of reactions noted up to the age of 5 years 92 % are classified as mild and 8 % as intense Even in cases where nailbiting is classified as habitual the reaction is still overwhelmingly mild.

Examples of attempts classified as intense include frightening corrections: "bad for your insides germs in your tummy" "ugly hands and nails "might have to go into hospital together with the purchase of a bitter-tasting substance (Finger-tip) painted on the nails. or a rap on the fingers

These countermeasures did not meet with any notable success Deteriorations and improvements are fairly evenly distributed, regardless of whether any action is taken or not The following figures can be quoted: Of 86 children noted for countermeasures at 4 and 5 years 18 showed a deterioration 23 an improvement and 45 no change at all at the next annual investigation. Reactions to nailbiting in older children (over 5 years) have not been noted.

SUMMARY

The age frequency of nailbiting the persistence of the symptom and its covariation with other behavioural variables up to the age of 8 years are illustrated by material from the longitudinal Stockholm study Symptom frequency rises gradually during the pre-school years

to approximately 5 % daily nailbiting during the first year at school The frequency at the same age rises to c 40 % if less than daily frequencies are included (= all degrees of frequency)

Girls bite their nails consistently more frequently than boys The sex difference is statistically significant at 5 and probably significant at 6 years

During the ages observed nailbiting is often a more or less periodic symptom but once the symptom has appeared it has a definite tendency to recur

No statistically significant relations can be established between the cessation of thumb-sucking and the commencement of nailbiting nor between school start and deterioration in terms of nailbiting Children regarded by their mothers as particularly defiant between 6 and 8 years also tend more than other children to be nailbiters This was the only variable among those tested in which the result of the established covariation was hardly coincidental Tendencies to stammering tics or other oral sucking and biting behaviour were not related to nailbiting The measures taken by parents to induce children of 2 - 5 years to stop biting their nails are generally of a mild nature The action taken, generally in the form of verbal correction to which threats of fright may be added does not eliminate the symptom more often than abstention from any action at all The aggressive response elicited by biting another person is contrasted with the gentle reaction of parents to nailbiting

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CHAPTER XI

RHYTHMIC MOVEMENTS IN INFANCY AND EARLY CHILDHOOD

RHYTHMIC MOVEMENTS IN INFANCY AND EARLY CHILDHOOD

HEAD BANGING HEAD TURNING AND ROCKING

INTRODUCTION

Children often develop a series of ritual and rhythmic movements in connection with falling asleep The rituals are performed conscciously while the child is awake as a pleasant and playful preparation for the coming sleep Rhythmic head turnings or rockings can occur when the child is awake and tired but they are more commonly associated with a lower degree of wakefulness The child is approaching sleep generally in the evening but also during night waking The intensity of these movements varies from single turns of the head on the pillow to rocking movements involving the entire body and causing the bed to *shake* *Sometimes the child s head knocks* against the headboard with a bump or with other rhythmical sound effects thus eliminating the line of demarcation between jactatio capitis and head banging. Otherwise head banging is generally taken to refer to the less frequent condition in which the child, fully awake bangs its head against the floor wall or end of the bed either because it is angry or because it seeks satisfaction.

In the present essay this distinction will be retained as far as is possible Interpretation has been assisted by the mother s description of situations in which rhythmic movements occur

Little has been written on the occurrence of these conditions The few previous investigations which it has been possible to track down have been concerned with retrospective information. Lourie (6) states that 15 - 20 % of the children in an unselected child clinic population had "rocked, banged or swayed in one form or another for longer or shorter periods Mothers in a randomly selected obstetrical ward population who were interviewed by letter two years afterwards stated according to de Lissovy (5) that 15 % of their children were or had been head-bangers The response rate in this investigation was 75 %.

An account will be given here of the occurrence and course of rhythmic head bangings head turnings and rocking in a sample comprising 212 randomly selected children in the prospective longitudinal Stockholm study Co-variation with habitual thumb sucking sleep disturbances external sleep conditions outbursts of temper and bruxism in certain ages will be statistically tested.

Method

Information on these forms of behaviour has been obtained from VI: 15 and VI: 21 from 9 months to 5 years The occasional and the definitive habit have been segregated except as regards head turning These conditions have no longer been enquired after under a special heading at six years and subsequently but the few children still retaining the habit at 4 and 5 years have been followed up until the age of 8

RESULTS

Frequency

The percentage distributions of the various forms of rhythmic movement are summarised in Table 1 and fig 1 They can occur simultaneously in one and the same child or as isolated symptoms Rhythmic head or body movements occur so frequently before and at one year that in this normal child sample the behaviour is the rule rather than the exception. Since there is no sex difference boys and girls have been combined in a single group

Table 1. Head turning head banging and rocking at various ages Percentage distribution (cross-sectional)

	9 mths (n=203)	12 mths (n=207)	18 mths (n=194)	24 mths (n=204)	36 mths (n=202)	48 mths (n=204)	60 mths (n=198)
Head turning	24	24	26	14	7	2	3 5
Head banging	28	39	30	13	4	4	2
Rocking	45	27	12	10	3 5	3 5	3
Any of these rhythmic movements	66	61	45	26	12	8	6

Rhythmic body movements are generally associated with tiredness or occur as a kind of rocking to sleep. They can last from a few minutes to a matter of hours. Movements connected with settling and bedtime behaviour are often repeated identically night after night during the period in which they occur On the other hand variations between individuals present a wide range of alternative methods of obtaining gratification or relaxation. Some children lie on their stomachs beating their foreheads against the pillow while others lie on their backs and beat their pillows with the backs of their heads Again some stand on all fours rocking and knocking their heads against the end of the bed while others stand or kneel or lie with their entire body rocking with a motion that may be either gentle or violent The bumps or creaks produced by repeated impact against the walls or the ends or bottom of the bed do not appear to irritate the child; the same cannot be said of those around the child, and there are liable to be complaints from the neighbours

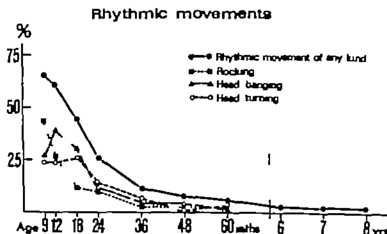


Fig 1. Incidence of rhythmic movements at various ages Percentage distribution. Cross-sectional figures

Apart from bedtime behaviour one and the same child can also indulge in head banging for other reasons during the day Some children exhibit no bedtime symptoms; instead they bang their heads exclusively during the daytime there being no apparent connection between

this rhythmic banging and any tiredness Sometimes head banging is provoked by an acute situation, when the child displays disappointment and anger or again during play or toilet training when the child is quite content and seeks amusement by banging its head against a wall a door or the side of the bath. In some cases the child displays pleasure during this behaviour or listens appreciatively to the sensation it creates in its head. The following table is the result of an attempt to elicit from mothers descriptions how many children resort to head banging in other situations besides obvious tiredness or settling down to sleep

Table 2. Head banging as an expression of anger or of happiness
Percentage of total number of head-bangers at different ages

	9 mths (n= 59)	12 mths (n= 81)	18 mths (n= 58)	24 mths (n= 23)
Disappointment anger	5	11	29	26
Sensation and/or happiness	20	15	10	9

Persistence

Any of the rhythmic movements mentioned above can occur episodically (mentioned only on one or two occasions during the investigation) while in other cases they can be reported as recurring year by year up to at least 8 years On page 78 is shown the number of times children have been reported as exhibiting at least one of the symptoms The estimate is based on a pure sample i e the children were not absent on any occasion during the investigation between 9 months and 8 years

Reported on one occasion from 9 months to 8 years		44
	two occasions	45
	three	30
	four	24
	five	5
	six	1
	seven	1
	eight	2
	nine	2
	ten	3

None of the children in the sample commenced its observed behaviour later than at the age of 18 months Most of the children began before they were one year old. Of the entire group only 7 began between 12 and 18 months

Six children (4 boys and 2 girls) or approximately 3 per cent of those investigated still rock rhythmically at the age of eight before falling asleep often hugging an object of some kind and humming in time to their rocking

Covariation-testing

Statistically speaking children still set in the habit of rocking at the age of three years are not more prone than others to habitual thumb sucking (X^2 = 0 111) nor are they considered particularly irascible (X^2 = 0 108) Once they have fallen asleep they do not as a rule sleep worse than other children (X^2 1 315) and they do not sleep in a separate room more often than other children (X^2 = 1.512) There is no relation to bruxism (X^2 = 0 805)

DISCUSSION

Unfortunately the children s rhythmic body movements were not systematically registered during the period preceding nine months We know from experience that this behaviour becomes more frequent during the second half of the first year of life as the child acquires more control of its muscular apparatus This is particularly true of rocking

movements performed by the child in a sitting or standing position and leaning against the edge of the bed. The frequently peak at 9 months indicated by the curve on page 76 is mainly due to rocking movements of this kind. Rhythmic head shaking and head turning do not attain their peak until 12 and 18 months respectively

Rocking is classed by certain psychoanalysts among the autoerotic infant activities of Freud s classical definition: these manifestations of sexual impulses can be recognized from the beginning but at first they are not yet directed at any outer object Each individual component of the sexual impulse works for a gain in pleasure and finds its gratification in its own body" (3) Spitz (7) has made a detailed study of rocking and other phenomena following observation of infants whose mothers were imprisoned for criminal offences In his view the condition is due to an emotionally unbalanced mother-child relationship The impulsive contradictory behaviour of the mothers precludes the development of normal object relations with the result that the child has to resort to narcissistic expressions of instinct Spitz observations refer to infants whose mothers are in prison and who lack normal contact with the outside world He finds that in 51 per cent of the 140 children at the institution rocking had been observed during infancy until 12 months The percentage incidence is not very different from that noted cross-sectionally in this normal child sample at 9 months (rocking = 44 % some kind of rhythmic activity = 67 %) Consequently it is hard to believe in the adequacy of Spitz interpretation of rocking as being due to the psycho-toxic influence of impulsively capricious mothers

The majority of rhythmic movement symptoms occur during infancy During this time the possibilities of object seeking movement are limited by the incompleteness of the neuro-muscular apparatus The majority of cases occur before the child can lift itself into all fours from a sitting or prone position or during the period when it can lift itself up given something to lean on but is uncertain of how to return to its former position Thus the first of these limitations is dictated by the level of the child s development When the child has developed a greater capacity for voluntary movement another limitation is imposed by the adults around it in the form of a high cot or

a playpen. In the event of frustration and heightened emotional tension, the motoric impulses provide a distraction and a safety valve Rocking provides a pleasurable form of relaxation when the child is tired. Different stereotypes repetitive rocking or swaying movements of the body or parts of the body can be observed in chronically ill antistic and CP children as well as the mentally retarded and blind. Rhythmic movement provides gratification and relaxation regardless of whether the obstacle to normal movement and contact with the environment is external or internal The growth obstacle disappears in normally developed children while in sick or defective children it is liable to persist In both cases habits may be formed as conditioned reflexes to particular often daily recurrent situations in the children s lives These are generally concerned with bedtime but they are sometimes solely connected with the sensation of tiredness

Escalona (2) observes the remarkable fact concerning physical autostimulation in infants that the same behaviour may sometimes have a calming effect while on other occasions or in other children it appears to cause excitement She also reflects that rocking and swaying produce the same kinds of sensations as the child often experienced in its mother s hands No doubt the use of cradles in earlier times was prompted by the realization that gentle rhythmic body movements had a calming effect Rocking has been used for centuries as a soporific and is still used today although the cradle has been abandoned owing to ambiguous assertions of its injurious consequences

It is interesting to see how the causes of head banging change with age The interpretations based on the situation described show that numerically head banging on account of anger or impotent fury undergoes a relative increase with increasing age Acute disappointment in a play situation or at bedtime become an increasingly dominant cause This behaviour too can crystallize into one of the child s typical reactions It bangs its head violently on the floor several times sometimes hurting itself in the process There is a striking resemblance here to other aggressive sel.-injurious symptoms Confined movement can of course be one of the causes of anger To this is added the sensation of helplessness. Relaxation and gratification are sought using the means available as in the following case A girl who has

disturbed her mother in a provocative manner every day is confined in a playpen. After reacting to her predicament by screaming and crying for hours on end the first few days she begin banging her head for hours on end instead. During the intervals between head bangings she sits and imagines things The thought of captive animals in cages and their rockings bangings and subsequent resignation is never far away (1) No fixation occurred in this particular case By the time the girl was 18 months old (6 months later) the symptoms had disappeared.

Apart from expressing despair head banging though generally in a somewhat milder form can also express happiness or a new pleasing sensation. There is no question here of disappointment instead the child has encountered a new acoustic or tactile experience which it can achieve on its own and which it is continually seeking with a gratified intrigued expression. Children who sit banging against the wall or the side of the bath while waiting to defecate during their toilet training presumably have mixed feelings in their quest for gratification.

EFFECTS OF LONGLASTING JACTATIO

Two of the cases in this study where rocking and turning in connection with falling asleep remained habitual until the age of eight years exhibited symptomload above average (see Ch. XVII) This applies only to such deviations as were noticeable to the mother since the personality tests carried out at the time have not yet been analysed. Nor have the many head-banging children suffered any noticeable injury as a result of their persistent habit This is in agreement with the Kravitz s study of 135 head-bangers (4) It is possible that in terms of environment and ability these children are not significantly different from children with other fixed early childhood habits Head banging during infancy is not a sign of retarded development autism or cerebral pares though these conditions are presumably more liable to produce self-gratificatory and self-injurious stereotypes

SUMMARY

A description is given of the occurrence of rhythmic movements such as head banging head turning and rocking in a longitudinally studied sample of 212 children At the age of three years 12 % of the children indulged in rhythmic movements of this kind and 6 % of them continued to do so at the age of five The stereotypes at three years exhibit no statistical connection with habitual thumbsucking night waking or bruxism, nor do children sleeping alone in a room exhibit more stereotypes than others

Headbanging occurs as a habit in connection with tiredness and settling at night and as an expression of emotional disturbance In some cases the child bangs its head to express happiness. Headbanging as a reaction to disappointment becomes relatively more frequent between the ages of 2 - 3 years

The behaviour begins mostly during infancy in a few cases between 12 - 18 months None of the children in this series began later than 18 months Six children (3 % of the 200 in the sample) continued their rhythmic rocking at bedtime without interruption until they reached school age In cases where the behaviour persists it is compared to a conditioned reflex in search of relaxation and gratification.

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CHAPTER XII

EXPECTATIONS AND REALITY CONCERNING TOILET TRAINING

EXPECTATIONS AND REALITY CONCERNING TOILET TRAINING

INTRODUCTION

The purpose of the following study of toilet training is to provide a general account of parental procedure the stage at which training begins and the final result: complete control of the bladder and bowels insofar as this materialises before the age of 8 years The essay will deal with the effects of early training of compulsion in connection with training and the relationship to certain behavioural variables in the child.

Many parents expect a great deal of toilet training and start early so as to obtain results as soon as possible The chronological relation between the commencement of training and control of the functions will be estimated for different groups of children. Continuing contact with the children has also made it possible to assess the stability of the capacity attained. The elements of compulsion occurring in toilet training have in certain quarters been ascribed considerable importance in the development of certain behavioural characteristics This will also be studied to a certain limited extent

The material also makes it possible to test the hypothesis that the individual rhythm displayed by the child at an early age (infancy) with regard to bowel function helps to determine the problems arising in connection with training (6) The regular child is supposed to be better placed to withstand the stresses of training without conflicts

The concepts of enuresis and encopresis are discussed in a later section. The differences between the primary and secondary forms are tested in different variables

C O M M E N C E M E N T   O F   T R A I N I N G

DEFINITION

The age at which the first effort is made to teach the child toilet behaviour is taken to mean the age at which special steps are introduced to adapt its evacuations to a particular time and place In order for training to be considered regular these efforts must have been made at least once a day and without any lapses.

Material and method

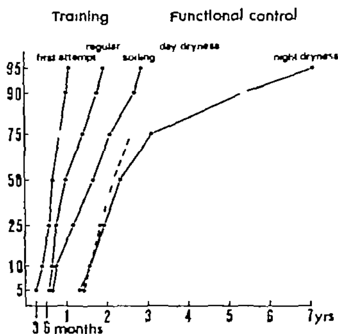
The material is derived from the prospective longitudinal investigation of the 212 randomly recruited children. Data from the stage of development at which training begins is in progress and concludes are always relatively recent so that there is comparatively little risk of events being remembered incorrectly The fixed form of the interview with its multiplicity of questions provides a good opportunity of endeavouring both qualitatively and quantitatively to capture the variable behaviour that precedes the full development of the function.

The variable questions on toilet training are to be found in interview form VI: items 30 - 46 In order to test differences relating to social class the median ages of children at the commencement of training in families belonging to the uppermost social class have been tested against those from the lowest social class (score 4 - 6 as against score 14 - 20 according to Graffar s modified scale) (7) Data concerning the composition of the family and the mother s education have been taken from the longitudinal social chart 1 - 3 years items 24 and 80 respectively

RESULTS

The first deliberate attempt at training in the sample is reported at 1 month, when a boy is regularly held out over a newspaper At 3 months 4 % of both boys and girls are being trained in a similar way by holding them out. At 6 months methods have begun to vary among those who have commenced training. Some are already being placed on a pot-chair and either supported by the mother or secured by straps The first lapses in training are also noted at this point. At 9 months between 40 - 50 % are sitting on a pot or pot-chair mostly the latter where the number of children secured by straps rises to attain its maximum at 12 - 18 months At 12 months the first reports are noted of use being made of the adults toilet presumably with assistance from an adult By the time they are 3 years old, over half the children have had experience of the ordinary toilet

7



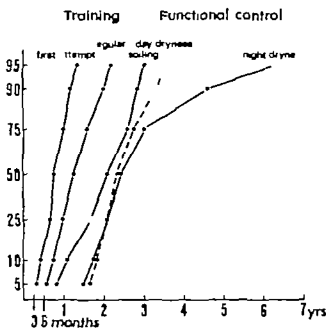


Fig 1. Cumulative percentile curves for the ages of training and functional control Plotted on normal probability paper
Upper picture refers to girls
Lower boys

l present cumulative percentile curves for the ages at which ining was first attempted and of which continuous regular trai- r started. The median age of the first attempt (see also Table 1 94 for the girls is 8 4 months with a range between percen- is 5 and 95 from 3 5 to 12.7 months The corresponding median for boys is insignificantly higher (9 months) with the first mpt for 90 % of them distributed between 4 4 months and 15 ths Thus training begins for perhaps just over half the child- before they can sit without a support by holding them out over pkin a newspaper pot or toilet

these early cases t is very common for a lapse to occur after time has been spent trying to devise a form of training that l produce results Continuous regular training can be postpo- several months by repeated lapses The median age for the girls 10 9 months and for the boys 13 9 months for the whole sample 3 months A significance test of the median age differences gives 05 (x^2 = 4 949)

ther the mother s education, the social status of the family previous experience of children bear any demonstrable relation the commencement of training. Relatively speaking there are as y children starting training before and after 9 months in fami- s where the mother has at least matriculated (education score 2) as in families with a lower educational standard (score 3 - 5) = 0 192) A similar random distribution with regard to early empts at training is also revealed by comparisons of first-born ldren and older siblings (x^2 = 0.012) The median ages for child- from families with different social scores according to Graffar s ision are given in Table 1 (page 94) The differences are negli- ble

DISCUSSION

rly commencement may reflect a high degree of confidence in success rough early training or it may stem from a less calculating habit tated by practical considerations A comparison of data obtained the same way from the longitudinal parallel studies in London ris and Stockholm has already served to show (4) that there are

considerable differences between mothers in culturally related countries The child in the London study is on average trained far earlier (median for the first attempt = 2 2 months) than the child in the present study The rather surprisingly early commencement of toilet training in London may be due to practical reasons namely the labour-saving effects of avoiding extra washing Disposable napkins are not used nearly as widely in London as in Stockholm. Consequently we are not entitled to draw any sweeping conclusions concerning the existence of different attitudes to toilet behaviour and different degrees of confidence in the efficacy of early training on the part of mothers with different habits in different societies. To the mothers in the present study however the use of disposable napkins is probably the simplest and most natural way of negotiating the problems of the first half year

The fact that regular training begins far later on average in the case of the boys is probably no more than another sign that they have greater difficulty in adjusting to training As will be shown in due course this reluctance often forces mothers to abandon training for long periods, and it is above all the boys who resist training This may be due to a difference in the maturity rates of the sexes

Ideas concerning the point at which toilet training should begin are clearly dictated by other factors than education and social background. Attitudes to toilet behaviour and disciplined training may have been established long before parenthood otherwise one might have expected different results from the more educated mothers. Yet during the last few decades there has been a considerable information campaign in the form of brochures and periodicals stressing the need for an adjustment of the pace of training to the individual stage of development It may be difficult for influence of this kind to prevail over attitudes acquired during childhood and adolescence

THE DEVELOPMENT OF FUNCTIONAL CONTROL OF THE BLADDER

DEFINITION

Doubts are sometimes raised as to the juncture at which full control of the bladder is attained. Periods of uncertainty and relapse into wetting are frequent Temporary behavioural regressions of this kind are taken into account here as with other functions connected with growth. A long period of observation is required before one can claim that full control (= practically always dry) has been attained. The percentile values in fig 1 are based on a follow-up of the function until one year s freedom from symptoms had been established. Relapses into wetting after this period have been classified as secondary wetting and have not affected the time given for primary control. As a result of this mixture of primary and secondary cases of inability to control the bladder the cross-sectional figures derived from investigations of wetting frequencies at specific ages are on a higher level.

Method

The data of functional control are obtained from interview form VI: item 39 and 40 Only the children described by their mothers as "practically always" dry have been included in the group with complete functional control unlike those who "usually" or sometimes are dry The graduation of 24-hour wetting frequencies provided by the interview answers provides scope for a detailed assessment

RESULTS

Daytime bladder control

Given the above criteria, the median age for day dryness (cf fig 1) for girls is 26 2 months and for boys 27 9 months The difference is not statistically significant (p =< 10) Despite the lack of significance in this material similar results have been obtained in other investigations (1 2) and the trend has invariably been the same.

Nighttime bladder control

The juncture at which night dryness is attained has been calculated subject to the same requirements as day dryness regarding the period of observation. In the case of children who have been woken during the

night (not those who have woken of their own accord) to pass water and have consequently avoided wetting their napkins or beds the juncture at which this arrangement ceased has been noted and taken as the time limit for night dryness Brief relapses of a temporary nature in connection with illness or special circumstances have been ignored in an overall assessment that a child has been dry practically the whole time The boys are also behind the girls (median ages 28 5 and 27 6 months respectively) as regards night dryness though the difference is quite small and not significant

W H E N I S C O N T R O L A T T A I N E D O V E R T H E B O W E L S ?

Method

The answers to column 38 of the interview form VI show the point at which the child gained control of its bowels The attempted structural grading of the frequency with which the child succeeds may appear exaggerated but it serves to define the degree of control. This gives a better picture of the functional fluctuations during the development period than would be obtained from mere affirmative and negative answers.

RESULTS

Bowel control is attained by the girls in the sample at a median age of 20 months and by the boys at 25.7 months (fig 1) An X^2 test of the median ages for the sex difference is significant at a level of 0 1 %.

There are children who have been reported clean from the age of 6 months and have never subsequently at least not up to the age of eight years soiled themselves. Other children fluctuate between success and relapse or do not succeed at all - particularly in the case of boys - in attaining the steadiness covered by a year s observation until they have almost reached school age

Thanks to their own attentiveness and their observation of signs given by their children, mothers can often achieve complete success in their efforts at toilet training for periods of half a year Children with congenital or acquired regularity of evacuation do not require anything like the same amount of supervision as others But even children who have thus avoided causing inconvenience for considerable periods can suffer relapses: the younger the child, the less certain its control.

Only 17 % of the children who at 9 months were regarded as having reasonable control of their bowels were noted for the same high degree of functional ability at each subsequent observation until the age of 3 years (12 18 24 and 36 months) Thus relapses are the rule and there is little possibility of predicting the juncture

at which steady control will be attained on the basis of conditions at 9 months

More confident predictions can be made in this respect at 12 months though even at this point little more than a third of the children in control of their bowels retain steady control throughout childhood (48 % of the clean girls and 31 % of the boys)

Corresponding predictions at 18 months regarding continued cleanness up to the age of 3 years are almost 100 per cent correct in the case of the girls while as yet little over half the clean boys retain steady control of their bowels.

Children who were clean at 24 months both boys and girls exhibited the same steady capacity at 36 months

Conclusion

Clearly the functional standard attained early represents a false security Girls achieve stabilisation at upwards of 18 months boys at upwards of 24 months The incapacity for complete bowel control which some children still exhibit at 4 years or which constitutes a regression after years of control (= primary and secondary encopresis) will be dealt with later in a special section.

DATA-SUMMARY IN TABULAR FORM

The median ages for the commencement of training and the attainment of functional control are summarised in the following table

Table 1. Median ages of first attempt at toilet training onset of continuous training day dryness night dryness and bowel control.

	Median age (calendar months)				
	First attempt at toilet training	Starting continuous training	Day dryness	Night dryness	Bowel control
otal sample	8 7	12 3	27 4	28.1	23 0
♂	9	13 9	27 9	28 5	25.7
♀	8.4	10 9	26 2	27 6	20 4
oo score at yrs of age Graffar)					
4 - 10	8 6				
11 - 13	8 9				
14 - 20	8 5				

THE RELATION BETWEEN THE DURATION OF TRAINING AND THE FUNCTIONAL CONTROL ATTAINED

A. DAYTIME BLADDER CONTROL. RESULTS

Table 2 contains a summary of the average time elapsing between the commencement of training and the achievement of steady bladder control during the daytime The division into groups according to the ages at which training began (before 9 months between 9 - 12 months and after 12 months) relates to the occasions on which the children were investigated.

Table ? Duration between first attempt at toilet training and *dryness* in the day

First attempt at training	Time differences between first attempt and day dryness (mean in months)		
	♀	♂	total
at and before 9 months	23 6	21	22 3
9-12	19 5	20 1	19 8
> 12	12.9	10 5	12 5
all ages	20 2 (n=86)	20 4 (n=120)	20 3 (n=206)

The average time difference between the first attempts at training and the point at which day dryness was attained is 20 3 months in the 206 cases where both items were available (1 case of cranio-synostosis has not been included 1 case is unknown and 3 cases were lost to the investigation before attaining day dryness) The corresponding figures for girls and boys are 20 2 and 20 4 months respectively

If instead we take as our starting point the point at which regular toilet training began dividing the children into these who were trained early and those who were trained late we obtain the result shown in Table 3 Since girls generally commence regular training earlier than boys (sex difference on the significance level of 5 %, cf page 88) and become dry somewhat earlier as well the points in time regarded as early and late vary between the groups

Table 3 Onset of regular training and attainment of day dryness

	Attainment of day dryness		
♀ (n = 6)	at 24 or before	later than 24 mths	
Regular training: before 12 mths	15	28	$\chi^2 = 0\ 607$
at 12 mths or later	17	26	
♂ (n = 120)	at 27 or before	later than 27 mths	
Regular training: at 15 or before	40	25	$\chi^2 = 0\ 200$
later than 15 mths	30	25	

This other basis of division also fails as regards both boys and girls to produce any statistically certain difference in attainment of day dryness between children receiving late and early regular training.

DISCUSSION

If control of this function were the result of training children trained early should achieve results after more or less the same spell of training as those trained later This does not seem to apply in reality Mothers leaving the commencement of training until after 12 months spend little more than half as much time on trai-

ning before their children become dry as those commencing training before 9 months Nor is there any definite connection between early or late regular training and the juncture at which day dryness is achieved. These results are far from surprising If the prospects of success in this respect are connected with the rate and schedule of the maturing of the nervous system, the nearer the commencement of training comes to the maturity stage the briefer will be the duration of training If we assume that training has no effect either positive or negative so that neuro-muscular maturity is the sole determinant of results the median value would suggest that this maturity is first attained by girls at the age of 26 months and by boys at 28 months If this assumption is correct then clearly a great deal of unnecessary labour is devoted to a function which will develop sooner or later without any training at all Since there are hardly any mothers who passively wait for this to happen, it is impossible to obtain comparative statistics which would show whether completely untrained children tend on average to become dry at the same time as trained children.

B BOWEL CONTROL

The median age for the first attempts at training was earlier found to be c 9 months (cf fig 1) The majority of children do not achieve steady sphincter control until shortly after 2 years

To ascertain the extent to which earlier training produces more rapid, permanent results the ages at which training began have been related to the ages at which steady control was achieved as in the case of bladder control

RESULTS

Girls who began training at 9 months or earlier tend on average to attain control somewhat - but insignificantly - earlier than those who are trained late (median ages 19 9 and 20 1 months respectively)

In the case of the boys however there is a clear difference between the median ages (early trainees - 25 1 months late trainees 27 7 months median test significant at the 2 % level)

The same relations are obtained when the commencement of continuous training is used as the basis of comparison (see Table 4) This comparison also indicates the probability of a positive relation between early training of the boys and the time at which bowel control is achieved (significance level $p = .05$)

Table 4. Onset of regular training and attainment of steady bowel control

	Bowel control		
♀ n = 86	at 18 mths or before	later than 18 mths	
Regular training: before 12 mths	19	24	x^2 = negligible
at 12 mths or later	14	29	
♂ n = 120	at 24 mths or before	later than 24 mths	
Regular training: at 15 or before	33	32	$x^2 = 4.770$ $p = .05$
later than 15 mths	17	38	

DISCUSSION

The co-variation of early training and early bowel control (which is apparent in the case of the boys but no more than inferable in the case of the girls) can perhaps be explained by the fact that training is more easily and successfully applied to the less frequent and usually more regular need that characterizes the bowel function. The attention given by parents to the child s indications and rhythm brings greater rewards during the training period even if the child lacks conscious control

R E A C T I O N S   T O   T O I L E T   T R A I N I N G

As already shown an early start to training means several months of fruitless work The child is called upon to co-operate at the very stage in its growth when self-assertion and the ego are becoming factors to reckon with. There are obvious risks of serious friction and adjustment difficulties In the following section a description and analysis will be given of the interplay or conflict resulting from this particular form of contact

__Method__

The interview sections dealing with toilet training procedure and the difficulties encountered make it possible for the child s reactions to be differentiated into various categories (interview form VI items 30 35 36 and 37) These categories range from active resistance via passive but disgruntled submission to a more neutral or positive acceptance Mothers have not always been able to give answers placing their children in a particular group because reactions have sometimes fluctuated between different degrees of resistance in some occasions and acceptance on others Since these children are not referable to either of the main groups they have been placed in a special category ("variable in Table 5)

Children s resistance to toilet training or their display of a lack of co-operation making training appear pointless for the time being can also be illustrated by the frequency of children whose training has had to be suspended for longer or shorter periods (VI: item 30:1) In order for a __lapse__ to have been noted in the interview training must previously have occurred for at least a week. Sporadic training attempts of briefer duration have not been included.

The attitude taken by mothers to the use of coercion has also been investigated, so too has their use of straps or belts either to support the child or to reduce its possibilities of escaping from the pot-chair This method has not been uniformly classified as coercive Clearly there is a difference of reaction between the child who accepts this and likes it and the child who bursts into tears and decamps taking the pot with him

The actual degree of coercion employed varies The procedure described in cases classified as coercive reflects an unflinching determination on the part of the mother often combined with threats or restrictions on the child s physical possibility of escaping from the toilet The child is replaced on the toilet repeatedly Sometimes irritation may lead to the child being held down or given a smack on the bottom. In a very few cases the child has been held on the toilet for up to 45 minutes Some cases report feeding du-

Sometimes the child will accede to its parents wishes and will consent, either under protest or lured by toys to stay put Often the adults realise that the situation is untenable and adapt themselves accordingly by suspending the child s toilet training for a time

Since the age at which habitual training begins varies the estimates of frequencies and differences are based solely on the number of children who have begun their training at the age investigated. The percentages for the age of 36 months are subject to an error in that training has terminated for a number of children but the deviations are related to all the children in the sample

The other variables used in the statistical analysis to ascertain possible relations to the use of coercion concern the mother s education (form 0 : item 80) the mother s occupation (form 0 (long) items 20:1 and 2) first-born children (form 0 (long) item 21)

The object in using coercion is presumably to inculcate regular toilet habits as soon as possible In order to investigate the positive or negative effects of this practice on the juncture at which control is achieved, the group of children reported at one or more investigations between 12 and 36 months as having been subjected to coercion (VI: items 37:8 9) has been compared with the rest The comparison relates to the point in time at which bowel control (before or after 24 months) and day dryness (≤ 30 months) were achieved and to the occurrence of sustained incapacity or a relapse into wetting or encopresis

The group of day wetting bed-wetting and encopretic children includes all those with uncertain control at 4 years or subsequently Separate estimates have been made for primary and secondary wetters.

RESULTS AND COMMENTS

The occurrence of different reactions by the children and of measures taken by the mothers has been summarised in Table 5 and fig 2 The variables examined are resistance suspension of training, prevention of escape from the pot-chair and the use of coercion by the mother when the child refuses to co-operate

Table 5 Responses and coercive measures in toilet training
(the percentage distribution is calculated on children in training)

Age in months	Number of children in training	Active resistance or passive displeasure VI:item 35: dig 5 6	Variable VI:35:9	Neutral or with pleasure VI:35:7,8	Cessation of training VI:30:1	Tied to pot-chair VI:30:4	Coercion VI:37:8,9
9	♀ 35	17	13	70	21	41	10
	♂ 48	19	10	71	36	50	12
12	♀ 72	17 ± 4.4	15	68	29	43	24
	♂ 90	34 ± 4 9	22	43	35	51	28
18	♀ 81	20 ± 4.4	30	50	26	21	20
	♂ 103	32 ± 4 6	26	42	42	44	23
24	♀ 84	8 ± 5	8	83	14	10	21
	♂ 115	27 ± 4	19	54	22	17	24
36	♀ 85	1	7	92	0	1	12
	♂ 121	2	7	92	3	1	15

Sex diff: active resist at 12 mths of age p 02
18 p 10 $\chi^2 = 3\ 536$
24 p 005
cessation at 18 " p 025
tied to pot at 18 p 001
coercion at all ages negligible differences

Girls of all ages adjust with less resistance than boys to the requirement of co-operation in training At 24 months the difference is significant on the 0 1 % level At this age more than 80 % of the girls are being trained without any problems arising while a considerable proportion of the boys are still unable or unwilling to co-operate

A special form of reaction is indicated by the data concerning retaining stools and defaecation afterwards (fig 2) In this sample only 3 two-year-old boys have been noted for retaining their faeces through fear of pain out of defiance or for other reasons It is far more common for children to defaecate immediately after the training session. Whether this is a gesture of defiance or due to a special functional incapacity it generally has a provocative effect It occurs in those apparently passively accepting training as well as in those who resist It is remarkable that one of every ten boys undergoing toilet training demonstrates his inability or unwillingness to co-operate in training in this way at the age of 18 months

Table 5 and fig 2 also show that on average the boys training has to be suspended more often than the girls The difference is probably significant (p = 025) during the observation period between 12 - 18 months The fact that no less than a quarter of the girls and nearly 40 % of the boys who had begun training by 18 months had to suspend it suggests that requirements and expectations concerning early toilet training bear little relation to the child s ability This incapacity is predominantly manifest in active resistance by the child (56 of the 64 suspensions of training that occurred between 12 and 18 months were due to resistance by the child)

The majority of mothers however show a more conciliatory and sympathetic attitude to the child resistance The different frequency curves in fig 2 often refer to the same children but with different reactions and different forms of parental action Nonetheless belief in coercion is so widespread that it was "usual at some point during the training period from 12 - 36 months for 23 % of the children in the sample If we add to these the number of children sometimes subjected to coercion in this connection, the percentage rises to over 40.

COERCION AND TRAINING RESULTS

There is nothing to suggest that coercion has a favourable influence upon the intended learning effect None of the group comparisons given below suggest that coercion yields early results (Table 7) Restrictiveness in connection with training at some point during the training period has been noted to a greater extent in children who are late in achieving day dryness (≥ 30 months) or are still day wetters after 4 years The same applies to bowel control though only as regards the girls It is worth mentioning that all four of the cases of primary encopresis included in the sample were subjected to coercion during their toilet training

Table 7 Coercive measures during some period of the toilet-training in relation to early or late bladder and bowel control enuresis and encopresis Both sexes (n = 206)

			χ^2	P
Coercive measures vs bladder control		(day ≥ 30 mths)	7 765	01
	bowel	(≥ 24 mths)	2.075	n.s.
"		♀	5 141	025
" "	"	♂	0 068	n.s
" "	primary diurnal enuresis		11.497	001
" "	nocturnal		0.859	n.s.
	secondary diurnal "		8.326	005
	nocturnal		0 029	n.s.
	encopresis (prim. + second.)		0.732	n.s.

DISCUSSION

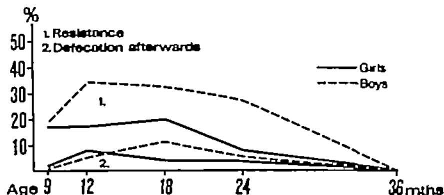
There is no reason to suppose that mothers are less anxious to inculcate regular toilet habits early in the boys than in girls. The later commencement of continuous training in the case of the boys is probably due to more widespread and adamant resistance on their part

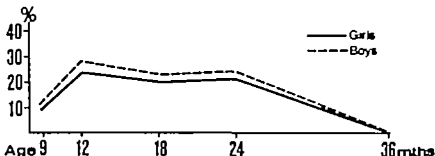
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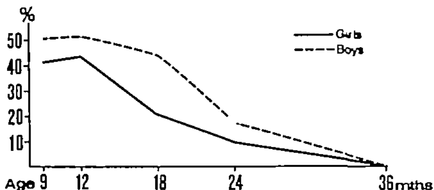
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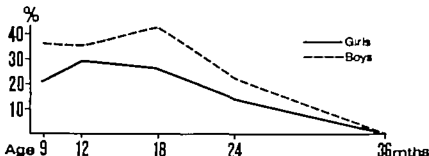


Fig 2 Incidence of coercive measures and children s responses in toilet training Percentage distribution. Cross-sectional figures

Above left = resistance and defecation afterwards

right = coercive measures

Below left = tied to pot chair

right = cessation in training

One might expect early training to increase the parents willingness to employ coercion since it remains fruitless for a relatively long period. This is not the case in the sample whether the limit for early training is put at 9 or 12 months During a certain period in training coercion is used with the same frequency in both groups As shown on page 105 it is above children who are late and unstable who provoke impatient and coercive reactions rather than those who begin their training early

Neither the mother s education her gainful employment nor her experience of earlier children produce significant differences in the use of coercion in toilet training (see Table 6) Although the frequency distribution suggest that the gainfully employed and first-time mother is less disposed to use coercion the tendency shown by the statistical analysis is within the limits of chance

Table 6 Occupational status and education of the mothers and the birth order of the children in relation to experience of coercive measures sometime between 12 - 36 months of age

	Experience of coercive measures sometime between 12-36 mths (number)	No such experience (number)	
M's occupational status when C is 1 2 and 3 yrs of age			
Full-time or part-time	11	25	X^2 = 1 617 n s
Other	72	99	
M's education when C is 3 yrs of age			
score 1 + 2	14	71	X^2 = 0 779 n s
3 + 4	15	100	
Birth order:			
First born	31	56	X^2 = 1 325 n s
Other	52	67	

COERCION AND TRAINING RESULTS

There is nothing to suggest that coercion has a favourable influence upon the intended learning effect None of the group comparisons given below suggest that coercion yields early results (Table 7) Restrictiveness in connection with training at some point during the training period has been noted to a greater extent in children who are late in achieving day dryness (≥ 30 months) or are still day wetters after 4 years The same applies to bowel control though only as regards the girls It is worth mentioning that all four of the cases of primary encopresis included in the sample were subjected to coercion during their toilet training

Table 7 Coercive measures during some period of the toilet-training in relation to early or late bladder and bowel control enuresis and encopresis Both sexes (n = 206)

		χ^2	P
Coercive measures vs	bladder control (day ≥ 30 mths)	7 765	01
	bowel (≥ 24 mths)	2 075	n.s
	♀	5 141	025
	♂	0 068	n.s
	primary diurnal enuresis	11.497	001
	nocturnal	0 859	n.s
	secondary diurnal	8 326	005
	nocturnal	0 029	n.s
	encopresis (prim. + second.)	0 732	n.s

DISCUSSION

There is no reason to suppose that mothers are less anxious to inculcate regular toilet habits early in the boys than in girls The later commencement of continuous training in the case of the boys is probably due to more widespread and adamant resistance on their part

The interpretation of the results concerning the co-variation of coercion and sphincter instability is quite unequivocal on one point only namely that the use of coercion in toilet training does not produce quicker or more reliable results But this does not necessarily entitle us to reverse the argument and say that failures are to be seen as a prolonged defiance symptom as has been suggested concerning encopresis (1 5) A child who for a particular reason or several interrelated reasons whether environmental or constitutional lacks the resources to adapt itself promptly to the demands made by adults often provokes them to stringent counter measures The slow maturing of this sector or the rhythmic irregularity which is perhaps an idiosyncrasy of certain children and slows down the learning process can easily provoke a different kind of treatment from that experienced by children who adjust more easily and are quicker to acquire regular toilet habits

According to arguments of this kind, then delayed maturity could occur relatively independently of training In other words children who are late in achieving steady control of the sphincter are also more liable to be subjected to coercive training whether the connection involved be simultaneous or causal It is however a truism that emotional upsets can affect learning and so long as restrictive treatment of the child in toilet training cannot be shown to have any positive effect there would appear to be no good reason for resorting to such a method.

THE RELATION OF COERCIVE TRAINING TO OTHER VARIABLES

INTRODUCTION

Conflicts in toilet training are liable to have undesirable effects in other sectors A daily activity generally associated with discomfort (which is how the child s behaviour is to be interpreted) may conceivably create an attitude of defiance and resistance covering a wider sphere than toilet training alone It may influence the entire climate of upbringing and manifest itself in symptoms in a variety of sectors A test will therefore be made of the hypothesis that children who have experienced coercive training tend more than others to exhibit deviations in so-called normal behaviour The main variables considered here are refusal to eat stammering tics nail biting and defiance as interpreted by the mother

Method

The data on refusal to eat used in the statistical analysis cover the ages of 1½ and 3 years i e a considerable portion of the training period. The attitude to the food situation mainly considered to reflect emotional dependence on the mother is that expressed in the otherwise healthy child by a general aversion to liquid or solid food or both. Selective refusal of food has in this context been considered less representative of the topic under consideration. Only children noted for such a general aversion to food at one more interviews during the period in question (form Y items 73:5 7 and 9) have been included to form a group contrasting to those not rejecting food to the same extent

There were 72 children (c 35 %) whose mothers considered them to have a general aversion to food at some stage during the period 1 - 3 years The symptom varies from one investigation to another so that refusal of food is seldom persistent The greatest percentage is reported between 1½ - 2 years when 16 % of the children were noted for food problems of this kind.

Concerning speech impediments data from 3 and 4 years sufficiently close in time to the training period have been chosen to elucidate any connection with coercive toilet training Children with non-fluent (stuttering") speech occurring during their third and fourth years have regardless of the intensity of their impediment been made to form a comparison group vis à vis the others The reader is further referred to the essay on speech impediments

Coercive toilet training has been similarly tested for co-variation with nail biting or with tics. Since both nail biting and tics are rare during the period in which training is in progress these va-

riables have not been applied until the ages of 3 - 5 years Nail biting has been restricted to habitual cases (relatively few) unlike tics where all the children with *involuntary tic-like symptoms* during the pre-school ages have been included in the comparison group regardless of the frequency of the symptom. (Form Y item 20 dig 4 - 9 and item 13 dig 7 - 9 only) The numbers of children with symptoms as defined used in the statistical comparison were as follows: nailbiting 26 and tics 68

Data from item 50 form Y have been used to see whether coercively trained children are differently distributed among children considered particularly defiant between 6 - 8 years Since a 5-point scale from 0 - 4 has been used in this variable and the defiance symptom has been liable to vary in different individuals from year to year a total score for each child has been used to represent the defiance value The maximum score for the three-year period 6 - 8 years is 12 (= considered consistently defiant) and the minimum 0 (= never defiant) Only children investigated every year have been included. Some 20 % of both boys and girls have scored a sufficiently high defiance rating" (between 7 - 10) during the three-year period 6 - 8 years to qualify for inclusion in the group of defiant children.

RESULTS AND DISCUSSION

The results are summarized in Table 8 The variables given in the table are compared throughout with the variable denoting the child s experience of coercive measures in toilet training

Table 8 Coercive measures during a period of toilet training in relation to feeding troubles speech disturbances nail biting, "tics" and symptoms of defiance

Variable		Test of significance		
			χ^2	P
Refusal of food during the training period			0 334	n s
Speech impediments (stuttering) at 3 - 4 years		♂	8 850	01
		♀	6 224	02
Nailbiting	at 2-3 years		0 466	n.s
Tics	3-5		2.224	n.s
Defiance symptoms	6-8		0 065	n.s

The only probable connection suggested by this material concerns the variable of non-fluency in speech. Reference is made in this respect to the essay on early speech impediments (page 145), in which the observation is discussed.

It has not proved possible to demonstrate the probability of the hypotheses that training involving coercion for a certain length of time results in reactions expressing defiance (nail biting, food refusal) affective motor tension (tics) or expressions of defiance remaining after the end of the training period. The findings presented here correspond in comparable parts to those of Hetherington et al (3) who stated "neither figure (in their investigation) supports the postulated relation of severe toilet training to high degrees of obstinacy orderliness and parsimony The same negative conclusion applies to the analytic emphasis on age of toilet training" In our investigation however it has only been possible to use the mother s view of her child s behaviour to evaluate this question. The extensive material from Rorschach and other testing methods designed to illustrate the child s personality structure has not yet been studied. The question of inapparent residuary effects on personality therefor must be left open for the time being.

REGULAR BOWEL FUNCTIONING AND ITS RELATION TO TRAINING

INTRODUCTION

Thomas et al (8) have found in the longitudinal New York investigation that children whose needs (food, defaecation, sleep) are regular from the outset adjust more easily to training when it is introduced. In order to test this theory on the limited sector relating to the regularity of the bowel function, children with different rhythms during infancy have been compared with regard to training resistance at 18 and 24 months

Method

Mothers have had no difficulty in specifying whether defaecation generally occurs at the same time every day or not and they have supplied information on this point at all five investigations during infancy (VI: items 23:0 - 9) The alternative answers to the question "Is it generally at the same time or ? are distributed on a scale of never seldom, sometimes usually

Relatively few children (n = 50) have been described as regular at practically every investigation and far fewer (n = 5) have been described as very unreliable The majority in between these extremes have been classifiable into predominantly regular and mostly irregular as regards defaecation times. The dichotomy of the material based on these principles gives a majority tending towards regularity (total n = 154) but at the same time a considerable irregular group (n = 55) The number of children actively resisting toilet training at 18 and 24 months respectively has been compared in the two groups with different degrees of rhythmicity of bowel function.

RESULTS AND DISCUSSION

The wide dispersion of the number of cases in the different groups can be seen in Table 9 A chi-square test for the differences shows at 18 months a random distribution and at 24 months a probable significance of the children described as irregular during infancy being more demonstrative of their aversion to training (χ^2 = 4 597 p = 05) There are no demonstrable sex differences

Table 9 Regularity in defecation during infancy in relation to resistance in the toilet-training situation at 18 and 24 months of age

Rhythmicity during infancy	At 18 months of age (numerical distribution) Active resistance variable cessation of training		Neutral or with pleasure		No information or no investigation at 18 resp 24		Total	
	♀	♂	♀	♂	♀	♂	♀	♂
Regular	29	45	36	32	6	6	71	83
Irregular	11	21	6	14	1	2	18	37
	At 24 months							
Regular	11	35	56	47	4	1	71	83
Irregular	4	21	13	15	1	1	18	37

It should be noted that changes in the regularity of defaecation are very common during the training period. Sometimes this change towards greater irregularity coincides with the commencement of training (37 cases) often it occurs later during the period for no specified reason (57 cases) The rhythm remained practically constant in 61 cases.

One can only speculate as to the cause of the unevenness thus reported. Either the mother did not succeed very well at the commencement of training in adapting her methods to the child s previous rhythm, or the child may have reached an age where attentiveness and incipient self-assertion are beginning to disturb vegetative functions In some cases regularity during infancy could make for less troublesome toilet training if the demands made of the child were postponed and made to accord with its earlier behaviour

B E D W E T T I N G   D A Y W E T T I N G   E N C O P R E S I S

INTRODUCTION

This section will be concerned with the frequency and interrelation of primary and secondary inability for sphincter control at different ages between 4 - 8 years The simultaneous occurrence of the different forms of functional weakness in individual children will be illustrated as will the connection between intelligence level and enuresis and encopresis

There is no standard definition of the concept of enuresis Generally the term is taken to mean involuntary wetting which in relation to the age at which it occurs constitutes a definite deviation from normal behaviour and is not connected with known organic changes. But the wealth of literature on the subject presupposes a variety of age limits. If children still in the habit of night wetting after the age of three years are to be termed enuretics c 25 % of this normal child sample would be classifiable as such, as can be seen from fig 1 page 87 It would seem to be a misuse of the term deviation to apply it to a phenomenon of such frequency A more stringent interpretation can be achieved by attaching the term to certain definite percentiles or standard deviations A working definition of this kind is appropriate as regards primary functional control Secondary enuresis which occurs after a sufficiently long period of demonstrable control is always a deviation from a normal state

The length of the observed symptom free period also affects the definition. An observer stipulating no more than about one month s sphincter control will obtain very different enuresis frequencies from the observer stipulating a year Uncertainty and temporary regressions are typical phenomena in the acquisition of growth-conditioned functions. A considerable period of observation is required in order to accommodate this uncertainty Before the control over the bladder is definitive there occurs a period of fluctuation which is obviously susceptible to influences of various kinds.

In this account of day and bed wetting information was collected on all forms of occasional, periodic or persistent inability to control the bladder Only those who lacked bladder control periodically during the year in question or at the time of the investigation are regarded as being day or bed wetters of practical importance. In those instances where incidences or calculations concerning intensity refer to wetting of a more occasional nature this is stated in the text

Encopresis is here interpreted as defined by Bellman (1) in her study of the subject namely repeated involuntary discharge of faeces in the clothes for no known organic reasons In order for such an event to be classified as encopresis it must above all have been noted in the investigation at 4 years or later up to the age of 8 years Since continual data have been collected the encopretic group has also been made to include children who have only been noted for occasional mishaps in one of the annual investigations but whose failures have been shown by a longitudinal study to be recurrent which suggests that their control of the function is uncertain.

Method

Since the formulation and gradation of the wetting variable in interview form VI items 39 and 40 at 4 and 5 is not altogether the same as at 6 7 and 8 years the contents of the digits have had to be transposed.

At 4 - 5 years item 40	digit	at 6 - 8 years	digit
never dry	0	never wetting	0
rarely	6	rarely	1
sometimes	7	sometimes	2
practically always dry		wetting several/week	3
wetting period since last visit	4	once or more/night	4
wetting occasionally since last visit	5		
always dry	9		

The following digits have been taken to correspond to one another:

at 4 - 5 years		at 6 - 8 years	
0 6 corresponds to		4 3	wetting every night or several/week
4 7		2	-wetting sometimes or periodically during the past year
5		1	-now dry at night but occasionally wetting during the past year
9		0	-dry at night since the last visit

A similar transposition has been effected with respect to the day wetting variable

The longitudinal course of the symptom will be illustrated starting from conditions at four years Subsequent annual changes among these children with wetting will be related to the simultaneous background of the cross-sectional frequency of wetting in the sample A pure samples has been used in the longitudinal account i e all the children in this account have been investigated on every possible occasion.

RESULTS

Night wetting

The frequency of night wetting of all different degrees of intensity and at different ages is given in Table 10

Table 10 Incidence of wetting in the night from 4 to 8 years of age (cross-sectional percentage distribution)

	Girls				Boys			
Age in year	n	Wetting every night or often	Wetting sometimes or periodically last year	Wetting occasionally since last visit	n	Wetting every night or often	Wetting sometimes or periodically last year	Wetting occasionally since last visit
4	85	3 5	8.2	9.4	119	4 2	10 1	16 8
5	82	1 2	3 7	12.2	116	0 9	5.2	12.9
6	83	2.4	3.6	14.5	117	2.6	6	17 1
7	81	1 2	3 7	12.4	114	3 5	4 4	12 3
8	81	1.2	2.5	7.4	115	3.4	1 7	9 6

The investigation at 4 years revealed that 55 children (= 27 %) had exhibited some uncertainty in their night control of the bladder during the past observation year Many of them however had only suffered mishaps on isolated nights and can to all intents and purposes be classified together with those who are always dry at night Those with intermittent periods of night wetting during the observation period or with wetting practically every night at the time of the investigation amounted to no more than 28 (14 %) The group prone to night wetting at the very time of the 4 years investigation numbered 15 children (9 ♂ and 6 ♀ making 7 % of the sample)

Night enuresis at 4 years is mostly of a primary nature Only one of the currently or periodically night wetting four-year-olds had previously had full control of the bladder for at least one year

The decline in the frequency of night wetting in the group of children who had been current or periodical night wetters at four years or during the immediately preceding period is illustrated in fig 3

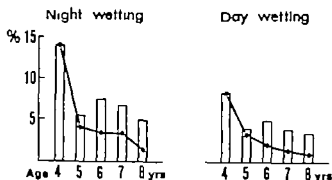


Fig 3 Cessation of night-wetting and day-wetting (= longitudinal curves) in relation to cross-sectional number (= bars) at various ages Percentage distribution.

The bars show the percentage of wetters of the same frequency degree calculated on the basis of the cross-sectional figures for the year in question. The percentage difference between the curve and the bars represents the number of secondary night wetters during these years.

The relation between primary and secondary enuretics changes from a predominance of primary enuretics at 4 years to the reverse at 8 years. In comparative figures are estimated for all night wetting children, i.e. including those exhibiting an occasional instability between 4 - 8 years the relation of primary to secondary night wetting is 1:2,5.

During these years night wetting is proportionally more prevalent among the boys than among the girls. At 4 and 5 years the percentage ratio is 1:1,2 at 6 years 1:1,4 at 7 years 1:1 6 and at 8 years 1:1,4. Girls are very little in evidence among secondary night wetters at any frequency level. A comparison of the distribution of boys and girls among those who have wet the bed occasionally or frequently during the observation period between 4 - 8 years reveals a statistical probability in favour of the boys predominance (X^2 = 4 600 p = 05)

Day wetting

The frequency of children with day wetting is given in the following table 11. It will be seen that frequent day wetting is less common than frequent bed-wetting whereas occasional instability in bladder control is noted considerably more often in the day than at night

The duration and the decline in the frequency of the symptom from 4 - 8 years can be seen from the curve in fig 3 as compared with the cross-sectional frequencies of the bars for the same ages

Table 11 Incidence of wetting in the day from 4 - 8 years of age (cross-sectional percentage distribution)

	Girls				Boys			
Age in year	n	Wetting every day or often	Wetting sometimes or periodically	Wetting occasionally since last visit	n	Wetting every day or often	Wetting sometimes or periodically	Wetting occasionally since last visit
4	85	0	9 4	25 9	119	0 8	3 3	15.1
5	82	0	3 6	23 2	116	0	3 4	18 1
6	83	0	6	19 3	117	0 8	4 3	18
7	81	1 2	4 9	16 1	114	0	2.6	7
8	81	1 2	2 5	14.8	115	0 9	2 6	4.4

Over one-third of day wetters aged between 4 - 5 years are secondary At 7 - 8 years the position is reversed with the secondary day wetters constituting two-thirds If all occasional day wetters are included the ratio of primary to secondary wetters is 1:6 for the whole of the age period 4 - 8 years

The distribution of the sexes is such that the girls tend more towards day wetting than the boys If all 4 - 8 year-old girls in the sample with occasional or persistent day wetting are compared with the corresponding category of boys the X^2 test gives a value of 4 997 (p = 05)

Encopresis

The incidence of encopresis in the material can be seen from the cross-sectional figures in Table 12.

Table 12. Incidence of soiling from 4 to 8 years of age (cross-sectional percentage distribution)

	Girls				Boys			
Age in year	n	Every day or often	Sometimes or periodically last year	Soiling occasionally since last visit	n	Every day or often	Sometimes or periodically last year	Soiling occasionally since last visit
4	85	0	0	7 1	119	0 8	4 2	9 2
5	82	0	2 4	3 6	116	0 9	0 9	5.2
6	83	0	1 2	2 4	117	1 7	1 7	6.0
7	81	1 2	0	2.5	114	0 9	3 5	4.4
8	81	0	0	2.5	115	1 7	3 5	2 6

Encopresis is generally slight amounting in the case of the children noted for occasional mishaps to little more than a slight soiling of their trousers roughly once or twice a month. The far greater intensity occuring in certain cases has also entailed not only a higher frequency but also a larger quantity of faeces in the trousers.

The ratios of primary to secondary forms are 4:1 at 4 years and 1:4.5 at 8 years This figures include all cases even those of occasionally encopresis. Three boys were reported at each annual investigation up to the age of 7 - 8 years as tending to soil their trousers. Another boy and one girl exhibited a similar persistent uncertainty of control but were symptom-free at 4 and 5 years

The duration of encopresis has been estimated against the background of conditions between 3 and 4 years and between 4 and 5 years All those habitually or occasionally exhibiting unsteady bowel control during this period have been followed up until the age of 8 years. The results are given in fig 4

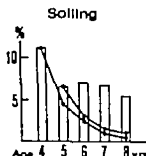


Fig 4 Cessation of soiling

The parallel curves in fig 4 denote the subsequent course of encopresis in the children noted for it at 4 and 5 years respectively regardless of whether it was primary or secondary in origin. Boys predominate on a percentage basis but the sex difference was not found to be statistically significant (X^2 = 2.925)

<u>Co-variation in different forms of instability of sphincter control</u>

There is a statistically clear co-variation of day and night wetting in both boys and girls If all primary and secondary day wetters between 4 - 8 years are compared with primary and secondary night wetters the number exhibiting both weaknesses is too great to be attributed to chance (Significance level for girls p = 02 for boys p = 005) <u>Primary</u> day and night wetting symptoms also display some co-variation but the number of cases investigated is too small to give a probable significance

Encopresis is also commoner in the night wetting boys (X^2 = 5 607 p = 02) and the day wetting boys (X^2 = 7 010 p = 01) than one would expect from a random distribution. No statistical relations have been established for the girls.

DISCUSSION

Comparisons of different investigations concerning the frequency of such phenomena as night wetting day wetting or soiling are hazardous since registration methods and the length of the symptom-free interval often vary Frequency data are sometimes based on information collected several years after the event If the incidence noted in a small material such as the present comprising 200 children agrees well with large-scale epidemiological investigations of a particular defined phenomenon this also speaks in favour of the reliability of the results which are specific to the longitudinal investigation procedure

Reference can be made to two large representative Swedish investigations of 7-year-old children Hallgren s from the mid 1950s (2) and Bellman s (1), which was carried out ten years later Both employ cross-sectional figures based on a questionnaire issued to parents. In one case the investigation covered 1 992 school-starters and in the other 8 683 Hallgren reports 6 6 % and Bellman 5 8 % enuretics the corresponding figures from this longitudinal study for 7-year-olds being 6 6 %. As the frequency diminishes year by year and Bellman s figures as she emphasises are based on children approaching their eighth birthday the three series would appear to agree well

In the study of primary enuresis carried out by the writer in 1955 (6) using longitudinal data but stipulating a shorter period of freedom from symptoms than has been adopted for the present study 4 % of the six-year-olds were found to be primary night wetters as against 4.5 % in the present investigation.

In Hallgren s study the incidence of day wetting at 7 years was 2.7 % for girls and 2.9 % for boys the former of these figures being considerably lower than the percentage (6 1 %) noted in this longitudinal study while the boys frequency is the same

As regards the incidence of encopresis comparison can be made with Bellman s comprehensive study She found on the basis of questionnaires and school medical cards an incidence of 1 5 % in children

with an average age of 7 $\frac{3}{4}$ years In the present investigation 6 children in the 7-year-old investigation and 6 in the 8-year-old investigation were registered as encopretics making 3 % of the sample at either age Bellman asserts that the frequency found by her is to be taken as a minimum. The differences may be due to the way in which information was obtained. As Bellman points out many parents are so embarrassed by soiling that they are reluctant to commit the fact of its occurrence to paper It is easier to give candid answers in a detailed interview with a psychologist one has known well for several years It should also be borne in mind that the percentages refer to a small number with the margin of uncertainty attributable to chance

The intensity of night wetting often varies even among those who are regarded as primary Weeks of nightly wetting may alternate with periods of several months during which only occasional mishaps occur Statements such as that made concerning a 5-year-old that the girl has not been dry one single night since she was born are more the exception than the rule This girl had been noted for persistent wetting at every investigation up to and including 7 years The strong element of heredity in this primary enuresis is evident from the statement that all of the mother s ten siblings had been bed wetters until between 5 and 10 years as had the mother s father and her paternal grandfather No systematic search has been made for hereditary elements in the occurrence of enuresis

Day wetting is a more occasional and varied symptom than night wetting In the case of the boys there is little chance of forecasting the course of the day wetting symptom during pre-school age A boy troubled by the symptom at 4 years runs only a slight risk of still being troubled by it when he starts school Any coincidence of the symptom with the ages of 4 and 8 years would seem to be coincidence and no more The chi-square comparison covers all forms of day wetting regardless of its frequency including the occasional wetters at 4 and 8 years. On the other hand, 8-year-old girls prone to day wetting (occasionally or frequent) include to a very great extent the same individuals who suffered from the symptom at 4 years (χ^2 test significant at a level of 1 %)

This difference is hard to explain, whether it is organic or due to the attitudes of those surrounding the child One should never lose sight of the fact that most of the day wetting occurring at these ages is an infrequent and predominantly secondary symptom. The few cases classed as primary i e unstable from an early age and with symptoms every year make little impression in a statistical comparison against the remainder of the day wetting group

Encopresis also occurs with such irregularity at these ages that one cannot possibly predict whether it will continue Of 11 children soiling themselves to a greater or lesser extent at 8 years only 4 had exhibited any symptoms whatsoever at 4 years Of the 6 reported as exhibiting relatively frequent symptoms at 8 years 4 had been found free of symptoms at the earlier age and had remained so for at least a year

COUNTERMEASURES AGAINST NIGHT WETTING DURING THE TOILET TRAINING PERIOD

The calmness with which parents await the gradual process of maturity at night stands in stark contrast to the zeal with which they endeavour to train the child during the daytime As a general rule (90 - 94 %) nothing is done to keep the child dry at 12 18 or 24 months Even if a child has still not achieved nocturnal bladder control by the age of 3 years it will as a rule be left alone (71 %) Sometimes (25 %) the child usually still half-asleep will be taken out of bed to pass water and will then go back to sleep It is very rare for children to resist the operation or to lie awake afterwards Presumably the use of napkins has reduced the eagerness of parents to get their children out of bed during the night

I N S T A B I L I T Y   A N D   I N T E L L I G E N C E

Method

In order to see whether the different groups in the sample with primary and secondary instability differ in intelligence from one another or from the rest of the sample the differences between mean standardized test scores at the age of 5 years have been tested for significance All degrees of instability from 4 years up to 8 years have been tested against each other while again the more frequently unstable have been tested against the occasionally unstable as shown in the table below Standardized test scores (Terman-Merrill) have been used for the comparison

RESULTS

The results are summarized in table 13

Table 13 Enuresis diurna, nocturna et encopresis in relation to intelligence quotient

			T-value	Degree of freedom	Significance
Day wetting (all) versus rest of sample			150	191	n.s.
Night wetting (all)			708	191	n.s
Encopresis (all) "	"		-1 168	191	n.s
Day wetting (all)	night wetting (all)		- 343	141	n s.
Primary day wetting	primary night wetting		278	31	n.s
	secondary	(all)	670	49	n.s.
night		(all)	405	62	n.s
Primary encopresis	encopresis		-1 676	11	n s
	primary day wetting		-2 217	11	p 05

DISCUSSION

No statistically significant deviations in ability can be demonstrated in the sample studied as regards the different forms of day and night wetting The only children significantly different from the

rest are the primary encopretics who are of inferior intelligence in comparison with children with primary day wetting It should be pointed out that this is a small group and its representativeness should be viewed accordingly

SUMMARY

The median age for the first attempt at training was 8 4 months for girls and 9 months for boys The median age for the commencement of continuous training i e the point after which there occurred no suspension of training was 10 9 months for girls and 13 8 months for boys A significance test of the difference in median age indicates statistical probability

Girls achieve daytime dryness at 26 2 months boys at 27 9 months Nocturnal dryness is achieved by the girls at a median age of 27 6 and by the boys at 28 5 months None of these differences satisfies the requirements of significance when statistically tested.

Girls are earlier in achieving control of the bowels (median age 20 months as against 25 7) The difference between the sexes is significant at the 1 % level

Children whose training began at an early age did not on average become dry during the daytime more quickly than children whose training was postponed until after 9 months Disregarding lapses of training it generally took 20 months from the commencement of training for steady results to be obtained

An analysis is made of children s reactions during the training period and of the mothers efforts to deal with them. The boys put up significantly more resistance during the period between 1 and 2 years and their training had to be suspended more often The peak is attained at 18 months when 25 % of the girls and 40 % of the boys who were being trained had to suspend it The majority of mothers took a sympathetic and exploratory attitude to the children s resistance but belief in the use of coercion is nonetheless so widespread that it was a common practice in the case of 23 % of the children in the sample during the training period between 12 - 36 months Neither the mother s education gainful employment nor experience of earlier children resulted in any significant differences in the frequency with which coercion was used.

The use of coercion in toilet training did not produce more rapid or reliable results in terms of functional control Children who who were late in achieving steady control of their sphincters ran a far greater risk than those who became dry at an early age of being subjected to coercive training

The hypothesis put forward that training including coercion for a certain period of time is reflected in other behavioural variables such as simultaneous refusal of food, tics during pre-school age or residual defiance symptoms after the end of training period has not been established as probable On the other hand the possibility of a connection between coercive training and early speech impediments cannot be discounted.

In the final section a description is given of the course and co-variation of primary and secondary forms of enuresis diurna et nocturna together with encopresis between 4 - 8 years Predictions based e g on conditions at 4 years regarding the state of the variable in question on the attainment of school age are very uncertain.

As regards intellectual test achievements using Terman-Merrill no differences in mean standardised quotients could be demonstrated between different frequency types of day and night wetting and other children. The few children with primary encopresis were of inferior intelligence to children with primary day wetting (significance 05)

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CHAPTER XIII

A PROSPECTIVE LONGITUDINAL VIEW OF EARLY SPEECH IMPEDIMENTS IN A NORMAL CHILD SAMPLE

A PROSPECTIVE LONGITUDINAL VIEW OF EARLY SPEECH IMPEDIMENTS IN A NORMAL CHILD SAMPLE

GENERAL INTRODUCTION

In spite of comprehensive and detailed studies the causes of stuttering are still unknown to us in many respects In his textbook on speech disorders in children Seeman (7) maintains that there are few pathological conditions with as many possible explanations as stuttering

During the years of childhood the impediments in children s speech presented by jerks repetition and stoppages are hard to distinguish from one another It is questionable whether this uncertainty coming as it does at a stage when the faculty of speech still lacks a sufficiently firm organization should be termed stuttering In his monography The Onset of Stuttering Wendel Johnson (5) distinguishes between non-fluency and stuttering In his view the occurrence of stammering in a child depends on the parents attitude to and evaluation of early irregularities in the child s speech. Once the suspicion has been aroused that the child is stammering the parents attitude changes. This is noticed by the child, whose uncertainty is deepened accordingly As a result of this interaction with the environment physiological irregularity of speech gives way to a self-generating rise in tension and an increasing speech disturbance which ultimately develops into stuttering But the majority of acute speech impediments are less dramatic and conspicuous in their origin Bloodstein (2) pointing to the episodic nature of early stuttering calls for longitudinal studies to elucidate the different phases.

There is no generally accepted definition of stuttering at the point where the symptom is still undeveloped. In the present account the term stuttering (stammering) insofar as it is used in stead of non-fluency in speech simply refers to a speech impediment observed by the mother and reported by her in response to the interview question: Does he (she) stammer at all? Thus the answer denotes that the child s manner

of fluent speaking has given rise to comment in some respect A working definition of this kind places certain limitations on the interpretation of the answers But great importance must always be attached to the observations which may have been made at home by the parents when dealing with such an irregular symptom as stammering particularly during its early phase The answers may also reflect an incomplete tentative but incipient mastery of the use of speech or again they may reflect an adjustment difficulty which frequently arises before a complex function becomes complete

The first part of the study will be principally concerned with the speech impediments observed in children in the sample between the ages of 3 and 8 years. The aim here will be to elucidate the prevalence of stuttering and to see whether this habit tends to persist or whether it is mostly a short-term phenomenon. Tests will also be made of certain relations to other variables which may be connected with the occurrence of stuttering The sections are headed: frequency persistence relation to accident and fright relation to speech maturity and the co-variation of speech disturbances and other behavioural variables

In the second part of the essay consideration will also be given to the incidence of retarded speech and enunciation defects in early childhood and in pre-school children.

IMPEDIMENTS IN THE FLOW OF THE SPEECH

Method

Speech impediments have been noted from the age of 3 years Data on the subject are taken from form V items 67 and 68 at 3 4 and 5 years items 46 and 47 at 6 7 and 8 years Other data used in the statistical analysis are specified in the various table headings and in the text At 6 7 and 8 years the interview question is somewhat differently phrased, namely: Has he repeated words or stammered? and Does he often get stuck on words?

FREQUENCY

Results and discussion

Table 1 shows the frequency of non-fluent speech.

Table 1 Incidence of non-fluent speech in various ages Percentage distribution. Cross-sectional figures

Age in years	Number of girls studied	Never stutter %	Occasionally %		Often %	Number of boys studied	Never stutter %		Occasionally %	Often %	Sex-difference Significance
3	85	82	14		4	121	73		22	5	p =< 20
4	85	84	15		1	116	72		20	8	p =< 10
5	81	92	6		2	115	78		17	5	p =< 02
			Seldom	Sometimes				Seldom	Sometimes		
6	83	83	10	7		117	67	15	15	3	p =< 02
7	81	80	16	4		114	60	26	12	2	p =< 005
8	81	81	11	7		115	71	17	12		p =< 10

The disturbance has been graded according to the frequency with which it occurred during the period immediately preceding the interview Frequency generally runs parallel to intensity When a child frequently demonstrates his speech disturbance it is also more conspicuous But intensity may also have undergone an acute rise in the year since the last report in children classed as occasional stutterers as were most of those affected

Boys constitute a proportionally greater percentage of those suffering from speech disturbances at each age: this is particularly the case at 5 - 7 years where the significance of the difference between the sexes is at least on the 02 level The result accords well with what has long been known concerning the greater proneness of boys to stammering (3 5)

PERSISTENCE

INTRODUCTION

The first signs of speech disturbance may predict a more conspicuous defect later on. When the children s doctor and child psychiatrist are confronted by the symptom as a subsidiary discovery during a general examination it is often overshadowed by other deviations These mild cases are seldom brought to the attention of the speech therapist since parents do not consider it necessary to consult him.

One question therefore concerns the extent to which the speech disturbances observed at 3 and 4 years respectively can presage stuttering later on. Are these disturbances a passing phenomenon? If not how likely are they to recur?

Results and discussion

Table 2 shows that the majority (60 %) of disturbances occurring for a time during the ages of 3 – 5 years do not recur at 8 years

Table 2. Number of children with recurrent speech disturbances up to 8 years of age after the onset at 3 4 and 5 years of age

First stammering		Frequence of recurrence 4	5	6	7	8 years
at 3 years	n=49x)	29	17	21	17	20
at 4		n=29	9	14	17	12
at 5			n=8	5	5	3

x) 2 of these children have since left the investigation (after 4 and 6 years respectively)

Temporary speech disturbances predominate in every annual investigation. Probably a large proportion of the many children noted for speech disturbances at 3 and 4 years are best compared to what are often termed "physiological stammerers i e their impediment can

be regarded as a stage in the development of the faculty of speech. In more than half the cases at this age the disturbance has disappeared within a year of its onset Of the disturbances beginning at 3 4 or 5 years 20 % recur only once during the observation period up to 8 years For these children the prospects are good as far as the present review extends Their disturbances have been temporary sometimes connected with specifically observed and stated situations of stress in which they have been involved.

28 children have been noted for recurrent disturbance in at least 4 annual investigations during the 6-year period. In the comparison of variables which follows below the group suffering from prolonged disturbance will be treated as a single unit The group numbered 23 boys and 5 girls The greater proneness of boys to speech disturbances is also reflected in the sex composition of this group (x^2 = 7 248 p = 01) The difference is significant

The group is heterogeneous as regards the intensity of disturbance The common factor between its members consists in the prolonged period during which the symptom occurred from time to time or at frequent intervals The group includes some children who have consulted a special clinic for treatment of their disturbances together with others for whom a specialist examination has not been considered necessary These children will subsequently be termed the group with prolonged speech disturbance The group will be tested against the other children to see whether there are any characteristics common to the experiences or qualities of those prone to stammering which are not merely attributable to chance

INTRODUCTION

Sometimes when reviewing individual cases one finds statements that the disturbance began in connection with frightening stressing or exciting events. Here are a few examples of causes given for stammering in children aged between 3 – 5 years Stammered for 1 week after an accident started with an eye operation (for cataract) after a stay in hospital after he had been crying when left alone for a long time one evening at home "when she started at day care centre stammered for several months after Christmas Sometimes the reason is thought to be that the child imitates a friend. Generally the mothers are unable to think of any reason at all

The idea that dramatic events or experiences of a frightening nature tend to affect speech has been established by direct observations of this kind of immediate consequences But fright and accidents are not uncommon during early childhood, though experiences involving marked anxiety reactions are clearly distinguished from many of the apparently more trivial mishaps that can happen in the normal ourse of things

Method

During each visit a note has been made of whether the children in the sample have been involved in serious accidents or have been seriously frightened by anything (V: 18) It is always difficult to assess the intensity of fright but the child s emotional reactions in connection with its fright have been marked in the mother s opinion. An assessment has been made both of the immediate behavioural reaction and of after-effects and notable conditions observed subsequently

Even if the mother has not been able to observe any definite chronological link a frightening experience may possibly increase emotional tension in such a way as to increase the disposition to stammer In order to see whether such a co-variation exists all children suffering from temporary or prolonged emotional disturbances after an accident and/or a reported frightening experience of some other kind have been compared with the other 3-year-olds for the occurrence of speech disturbances Since separation from the home coupled with admission to hospital or a children home often results in emotional stress at this age children with experience of this kind at 3 years have also been included in the group Tense relationships with parents or other more elusive environmental influence have not

been included since this would hardly be feasible at the present stage of analysis of the material

The 78 children reported as non-fluent in speech at 3 - 4 years have thus been divided into three groups: group 1 (11 cases) where the disturbance has been immediately related in time to clearly specified reasons group 2 (21 cases) where the disturbance has appeared without any known relation to an accident and/or frightening experience occurring during the previous period (see below) and group 3 (46 cases) where speech disturbances have appeared without any of the above combinations

Results

First a few words concerning the frequency of frightening experiences noted at the ages of 3 - 4 years and their visible after-effects In one of every 7 children involved in a situation of this kind (12 of 87 children at 3 or 4 years or both ages) the mother has in her own opinion discerned unmistakeable signs of a prolongation of the emotional upset caused by the fright In the other children who have had isolated upsetting experiences the after-effects have generally been of brief duration that is to say they have not appeared in such a way that the mother has been able to observe comprehend or report them.

Five of these definitely frightening incidents were clearly related in time to the onset of stammering In five other cases the reason has been thought possibly to lie in the child s separation from the home in hospital or with strangers In one case finally the boy started stammering after corporal punishment Thus a causal connection with definite emotional tension has been found possible in a total of 11 of the 78 cases where speech disturbances first appeared at 3 or 4 years

The incidence of known frightening experiences in stutterers and non-stutterers is shown in Table 5

A comparison between groups of children with and without speech disturbances reveals a fairly even distribution of registered accidents When all the boys investigated at both 3 and 4 years are included in the X^2 test the value of X^2 is 0 038 = n.s The corresponding value for the girls is 1 365 = n.s If the stuttering children whose etiology assumed known (11 altogether) are excluded from the statistical

Table 3 Non-fluency in speech at 3 or 4 years and its relation to accidents during the corresponding observation years

	Boys number	Accidents fright	Girls number	Accidents fright
Speech disturbances first appearing at 3 or 4 years	52		26	
Probably known cause	8	4	3	1
No known cause	44	14	23	7
No speech disturbance at 3 or 4 years	66	24	54	24
Not investigated at 3 or 4 years	4	-	10	-

estimates the X^2 values are 0 240 and 1 362 respectively

Table 4 shows the results concerning a possible connection between the persistence of speech disturbances and the known circumstances attending their onset according to the group division described on page 135

Speech disturbance beginning more or less dramatically at 3 or 4 years in connection with a likely and known cause do not tend to recur more than speech disturbances beginning in a different manner Children with persistent disturbances (= disturbances noted on at least 4 investigations between 3 - 8 years) tend rather to recur more frequently in the group where no definite chronological connections have been specifiable the proportions being 2 of 11 and 23 of 67 respectively However the difference is not significant

Table 4 Number of children with recurrent and persistent speech disturbances in groups of different etiology

Onset of stuttering at 3 or 4 years		Frequency of recurrence at 5 yrs	6 yrs	7 yrs	8 yrs	Persistent stuttering gro
Known incident chronologically connected with onset	n=11	3	4	4	3	2
Known incident not chronologically connected with onset	n=21	7	8	8	8	5
No known incidents at onset	n=46	16	23	22	21	19

DISCUSSION

A temporary frightening experience is probably capable of producing an acute speech disturbance if it is powerful enough but this disturbance does not last longer than stuttering due to other reasons nor can any concealed rise in tension following the fright be demonstrated in the background to speech disturbances The cases of stuttering which have occurred during the year in which the accident happened but without being related in time to the fright could equally well be due to coincidence

FON - FLUENCY IN SPEECH IN RELATION TO SPEECH MATURITY

INTRODUCTION

It is widely supposed that stammering and retarded speech are often connected in some way A greater risk is supposed to exist when the natural uncertainty of the first efforts at speech occurs at a more self-conscious age or when parents are tensely expectant regarding the course of speech development Delayed speech development and speech disturbances might also be expected to arise from a common cause in the form of a defective speech centre

Method

Speech maturity has been psychologically assessed on a 5-point scale during the investigation of the child at 3 and 5 years The assessment has included the scope of the child s vocabulary and how it is used the length and complexity of sentences and the child s ability to communicate successfully Rating 1: single words only Rating 2: elementary sentences seldom exceeding three words or a few longer utterances interspersed with jargon. Rating 3: sentences up to six and seven words Still some difficulty in making meaning clear Rating 4: simple sentences often incomplete but adequate for most practical purposes Rating 5: mature correctly worded sentences with a vocabulary ahead of the average

The mother s opinion of her child s speech is dealt with on page 150 below together with the account of enunciation defects

The following concerns the psychological assessment of speech maturity and the relationship of this maturity to disturbed speech flow

Results

The percentage distribution of the different ratings is shown in Table 5.

There is a clear difference between the sexes at 3 years with the girls developing earlier than the boys This difference has disappeared by the 5-years assessment

The relation between speech maturity and speech disturbances is shown in Table 6

Table 5 Ratings of maturity of language at 3 and 5 years of age Percentage distribution.

	Maturity of language at 3 years of age		at 5 years of age	
	♀ n=85	♂ n=117	♀ n=80	♂ n=115
Rating 1	1	3	0	0
2	17	29	8	4
3	49	50	55	57
4	24	15	34	37
5	9	3	4	3

Table 6. Speech maturity at 3 years and its relation to speech disturbances.

	Maturity of language at 3 years of age	Number	Non-fluency in speech at 3 or 4 years	Prolonged speech disturbance
♀	Ratings 1+2	15	4	1
	3+4+5	70	21	3
	(not investigated)	(5)	(1)	(1)
♂	Ratings 1+2	37	16	5
	3+4+5	80	33	16
	(not investigated)	(5)	(3)	(2)

This investigation does not corroborate the supposition that delayed speech development entails a greater risk of stammering The group noted for poor speech maturity at 3 years (psychologist s rating 1+2) does not contain significantly more cases of speech disturbance at 3 and 4 years than the group with average and good speech maturity This applies to both boys and girls (X^2 = 0 025 and 0 respectively) Nor do the boys noted for poor speech maturity at 3 years constitute a significantly larger proportion of the prolonged stammering group than other boys In the case of the girls the number of observations is too small to justify a separate estimate Both sexes taken together give no significance for delayed speech maturity increasing the proneness to prolonged speech disturbance symptoms

CO-VARIATION OF STUTTERING AND OTHER VARIABLES

INTRODUCTION

Although stammering is sometimes caused by established emotional factors in which anxiety plays a prominent part there is no definite explanation for most of the speech disturbances occurring in the present series In order to test the theory advanced in psychoanalytical literature that unpleasant oral sensations are capable of producing stammering children who have had weaning trouble have been compared with others with regard to stammering tendencies (V: items 57:7 8 and 58:7 8)

Other variables which may be associated with oral disturbances have also been compared with the occurrence of speech disturbances Thus deviations concerning appetite and coercion connected with refusal to eat prolonged thumb-sucking and nail-biting have been selected as test variables The children s experience of coercion during toilet training enuresis and encopresis genital play tics temper tantrums shyness and a number of social variables have also been used to elucidate possible connections

Method

The contents of the different items used in testing the variables can be summarised as follows.

Poor appetite: the group includes children noted in more than half their visits at the ages of 1 1½ 2 3 4 and 5 for what their mothers regarded as poor appetite (V: 31:6 7)

Coercion connected with refusal to eat: the countermeasures employed by mothers in the event of refusal to eat included: verbal insistence threats of punishment physical force and punishment (V: 78: 5 6 7 8) The investigation data used in this variable refer to the ages of 9 12 18 and 24 months) The use of threats punishment or coercion of any kind at any of these ages has qualified the child for inclusion in the coercion group for purposes of comparison

The prolonged thumb-sucking group includes children noted for definite habit of finger-sucking until at least the age of 5 years (see separate essay on fingersucking) The same limit applies to the nail-biting symptom (see separate essay)

The age for coercion during toilet training has been set between 1-3 years A detailed description of toilet training methods will be found in a separate essay

Stuttering tendencies in children with primary enuresis after the age of 4 years have been compared with those of children without primary enuresis. Children with day wetting (primary + secondary) between 6 - 8 years have been related in terms of speech disturbance to children of the same age not prone to day wetting The age limits for encopresis have been fixed at 6 - 8 years Children soiling themselves at these ages have been compared with those who are consistently clean.

Data on children with tic-like spasms and the simultaneous occurrence of stuttering refer to the ages of 6 - 8 years

Mothers observations concerning the boys manipulations of their genitals are so common that attention has been confined to the most frequent instances (V: 36: 2 3 4) at two of three visits between 6 - 8 years. For girls data have been obtained from V:36: 2 (all)

Real outbursts of temper tantrums between the ages of 3 - 4 years (VII: 55:9 at 3 years and VII: 54: 7 8 9 at 4 years) and particular shyness between the ages of 6 - 8 years (V: 60:2 - 4) have been related to speech disturbances in the ages concerned.

The social variables tested have comprised social class status at 3 and 4 years (0 (long): 76), the mother s education when the child is 3 years old (0 (long): 80) birth out of wedlock (0 (long): 17) and the birth of siblings (0:63) when the child was 3 - 4 years old.

Results

The significance of differences between the variables according to a χ^2 test are summarised in Table 7

Table 7 Speech disturbances in relation to various behavioural and social variables

		Prolonged stammering	Onset of stammering at 3 and 4 yrs	Stammering at some point between 6–8 yrs
Weaning troubles	♀	n.s		
	♂	n.s		
Poor appetite (1 5 years)	♀	too few obs		
	♂	02		
Coercion on refusal to eat (9–24 months)	♀	too few obs		
	♂	n s		
Prolonged finger-sucking	♀	n.s		
	♂	n.s		
Prolonged nail-biting	♀	n.s		
	♂	n.s		

		Prolonged stammering	Onset of stammering at 3 and 4 yrs	Stammering at some point between 6–8 yrs
Coercion during toilet training 1–3 years	♀	n.s	02	
	♂	n.s	01	
Night wetting > 4 years (primary secondary)	♀	too few obs		
	♂	n s		
Day-wetting (at 6–8 yrs)	♀			02
	♂			n.s
Encopresis (at 6–8 yrs)	♀			n s
	♂			n.s
Genital play (6–8 yrs)	♀			05
	♂			02
Tics (6–8 yrs)	♀			02
	♂			01
Temper tantrums (3 and 4 yrs)	♀		05	
	♂		n s	
Shyness (6–8 yrs)	♀			05
	♂			n.s
Social status at 3 years (acc Graffar)	♀		n.s	
	♂		n.s	
Mother s education	♀		n.s	
	♂		n s	
Birth out of wedlock	♀ + ♂	n.s		
Birth of siblings (2–4 yrs)	♀ + ♂		n.s	

Comments

The relation of prolonged stammering to weaning troubles is attributable to chance (X^2 = 0) This applies equally to children weaned from the breast and those weaned from the bottle Even if the entire group temporarily affected by speech disturbances during the ages of 3–8 years is compared with the other children the X^2 value is non-significant (X^2 = 1 716) Thus it is not possible using this technique on this material to establish a probable connection between weaning troubles and stuttering according to our working definition.

Poor appetite in the boys group is accompanied by speech disturbances far more often than one would expect from a random distribution (p = 02) The girls in the stuttering prone group are too few for a comparative estimate to serve any useful purpose

Although stuttering occurs relatively more frequently in boys subjected to coercion on refusal to eat during a considerable proportion of the speech development period the difference between the groups may be of a random nature (X^2 = 2 516)

The children in the sample whose behaviour during toilet training led to coercion (examples in the report on toilet training) are more prominent than the others among those noted for speech disturbances at the ages of 3 - 4 years (p = 01 for boys and 02 for girls) The same tendency can be observed in children with prolonged speech disturbances but it lacks significance (p = 20) However this lastmentioned group of children dominated by children whose speech disturbance began long after the conclusion of their toilet training

No connection with the speech disturbances considered here can be established for the primary enuretics nor for the children who reverted to night wetting after the age of 4 years The girls with day-wetting aged between 6 - 8 years are represented among those with speech disturbances to a greater extent than the others (p = 05) The comparatively few children (n = 19) with uncertain bowel control (encopresis) between the ages of 6 - 8 years are not represented among the children in the sample with speech disturbances at this age to a greater extent than can be attributed to chance

Children with facial twitches or other forms of tic generally mild and classed as temporary were on the other hand frequently noted for speech disturbances between the ages of 6 - 8 years This applies equally to boys and girls The level of significance is high (p = 02 and 01 respectively) Since the speech disturbance is seldom described as being so extreme as to involve accessory muscular movements there is probably no question of the tics symptom having been incorrectly diagnosed.

Equally remarkable and significant is the way in which these speech disturbance symptoms occur in children both boys and girls, of between 6 - 8 years who sometimes or frequently play with their genitals Insofar as both symptoms are expressions of emotional tension this phenomenon is merely two sides of the same thing with a common causal background. Since the parental reaction to genital play has not been investigated at these ages it is impossible either to affirm or refute the speculation that uncertainty of speech is a consequence of repeated unpleasant reactions from those around the child.

Non-fluency in speech does not co-vary significantly with thumb-sucking nail-biting coercion of refusal of food shyness (boys) or temper tantrums The variables have been tested at slightly different ages as can be seen from Table 7

The social variables tested have not revealed more than a random distribution of speech disturbance cases

DISCUSSION

Of the variables which have been tested poor appetite coercion during toilet training tics and childhood genital play are significantly evident among children with speech disturbances The implications of these relations are not unequivocal Toilet training generally proceeds during the speech development period. The mothers own statements concerning coercion reflect a special attitude during this period Of course a mother using stricter methods on her child in one respect will not necessarily have the same belief in constraint in every other aspect of training but there is no denying the latent diffusion in these cases since bowel control requires daily attention and can accordingly provide a wealth of occasions for conflicts leading to emotional tension in the child

In his monography concerning the onset of stammering mentioned earlier Wendell Johnson also found that children with non-fluent speech have been subjected to a significantly higher degree of coercion during toilet training than the control children with whom he compared them. His opinion that stuttering is produced by the interaction previously described between mother and child leads him to conclude that

both speech disturbance and coercive toilet training are due to the greater expectations parents have of their children. They expect the children to be clean at an early stage just as they expect them to be early in developing perfect speech. Presumably heavy demands on the child leave their mark on both variables

This explanatory model can presumably also be made to accommodate co-variation with eating difficulties tics and masturbation. The parents perfectionist aspirations which are incompatible with the behavioural variations of early childhood generate emotional conflict reactions in the child

In my opinion coercive training is one of several causes of heightened emotional tension. Disagreements resulting in emotional conflicts are the common factor which can result in speech disturbance as well as nervous twitches refusal to eat and an increased tendency to genital play These symptoms are merely different expressions of the same emotional tension. There is nothing in the present investigation to contradict the theory put forward by Bloemel (1) that stuttering begins as a stress reaction (primary stuttering) Acute or prolonged stress of sufficient severity will disorganize speech. Further case studies may serve to show whether the physical and emotional reactions (= secondary stuttering) displayed by older children as a result of the unpleasant sensation of not being able to speak distinctly serve to maintain stuttering and develop it

E N U N C I A T I O N   D E F E C T S

INTRODUCTION

A parent is daily reminded of his or her child s speech development Both stammering and incorrect enunciation are easily observable symptoms Their occurrence can often be established without the aid of any special devices or instruments They are most adequately noticeable in the home with its wealth of natural opportunities of contact and its shifting moods and emotions A certain capacity for observation and knowledge of the basic elements of development are however necessary in order to discover the mild forms

All children exhibit enunciation defects (physiological dyslalia) during a certain stage of their speech development These defects disappear at different times in different children depending on their growth. Delayed speech maturity combined among other things with enunciation difficulties may be symptomatic of late overall development with which it may run parallel It may also be isolated and principally or exclusively connected with language If one has the opportunity of following a group of children who have had difficulty in making themselves understood e g at 3 years it is often found that deficiencies in their capacity for self-expression are gradually reduced to certain special sounds instead of applying more generally to enunciation, vocabulary and sentence formation as was initially the case But apart from these enunciation deficiencies conditioned by development cross-sectional investigations e g at 4 5 or 6 years also reveal enunciation defects in other children which have never been observed previously The first of these could be classed as primary enunciation defects and the second as secondary The secondary type is probably due to other causes than delayed general development or retarded special speech development It has occurred in a child previously found to be on a level with the speech development of other children of the same age

An account of among other things speech development as measured by Brunet-Lezine s psycho-motoric development test and Terman-

Merrill's intelligence test during the first 5 years in children in this longitudinal study has previously been published by Klackenberg-Larsson and Stensson (4) The present account deals with the frequency of articulation deficiencies together with changes in these up to the age of 8 years.

The relation of this frequency to environment variables will be investigated and the complex relationships to testing or to measured intelligence quotients will also be elucidated with the aid of several years follow-up.

In an intelligence test that is based on verbal capacity to such a great extent as Terman-Merrill, enunciation defects and delayed speech maturity should have a certain influence on the achievement levels measured. Insofar as the handicap revealed by the test at 3 years is due to a specific speech retardation, the improvement that comes with increasing age should reduce its effect on the test result The extent to which this happens will be tested by comparing the mean scores at 3 and 8 years in groups of children with and without previous enunciation defects.

In connection with clinical observations tests are made of the following hypotheses concerning the relationship between retarded speech development and other variables:

(a) Speech development is more favourable in families where there is early verbal influence and linguistic stimulation than in families with no such stimuli.

(b) Children with retarded speech development are more prone than others to be temperamental and to display destructiveness, the presumed reason being desperation and anger in the face of the inability of others to understand what the child is attempting to convey by its speech.

Method

In order to arrive at a general idea of how capable the 3-year-old child was of using speech to make itself understood, above all by

those in its immediate vicinity the mothers were asked if they could understand everything their children said The question is general but functionally oriented. The difficulties cover a variety of conditions: inarticulation baby talk poor enunciation. If the function is so poor that even the child s parents cannot understand everything it says the specified articulation defects (lisping etc) are of less consequence Their specificity do not appear for suitable judgment until between 4 - 5 years

The child s speech difficulties are registered e g in interview form V: item 65 at 3 years V: 68 at 4 - 5 years and V: 47 at 6 - 8 years

At the same time as the child was tested a psychological assessment was made at 3 and 5 years respectively of enunciation and speech maturity (form 8: items 35 and 36)

Both assessments were based on a structured 5-point scale with 1 and 5 denoting the lowest and highest levels of development respectively Enunciation has been assessed in terms of the clarity and correct enunciation of the words used regardless of vocabulary and syntax

Rating 1: Mostly unintelligible

Rating 2: Difficult to understand owing to many faulty sounds or to pervading tendency to mumble

Rating 3: Most utterances can be understood but are either not very clearly spoken or are subject to three or more pervasive childish faults of enunciation

Rating 4: Generally clear One or two pervasive childish faults or occasional lapses; or a faulty system of enunciation taken over from adults involving slurred or missing consonants

Rating 5: Clear correct speech sounds throughout

Concerning the grounds for the assessment of speech maturity the reader is referred to page 138 where a description is given of its relation to stammering.

The content of ratings as regards both enunciation and speech maturity is in accordance with an internationally compiled model and based on collaboration by the study groups

As can be seen from the description of results below the distribution of children with different rating scores is such that estimates of differences are made more manageable and meaningful if they are divided into three groups (in some contexts only two)

A. Children who are hard to understand owing to considerable enunciation defects (ratings 1 and 2)
B. Children who speak indistinctly but intelligibly (rating 3)
C Children with more or less correct and well-developed articulation (ratings 4 and 5)

For purposes of analysis the children will therefore be divided into groups A, B and C (As regards the speech maturity variable the ratings will be similarly aggregated to three groups instead of five)

Bean Terman-Merrill quotients

In order to ascertain any connections or co-variations between the mother s education the parents reading activity together with the children and the latter s disposition to temper tantrums and destructiveness use has been made of the following items: from social form 0 (longitudinal): item 80 from form VII: item 36 and items 55 and 58.

FREQUENCY SEX DIFFERENCE

Results and discussion

The children in the sample noted at the age of 5 years for indistinct speech but not generally occasioning any serious problems include a girl whose hearing was so defective that the speech function may have been affected. The simultaneous somatic investigations have not revealed any signs of anatomical change in the organs of speech in any of the children No systematic audiological or phoniatric investigation of the sample has been carried out

The mothers opinions of their children s speech development at 3 years is shown in Table 8

Table 8. The mother s opinion of the child s speech at 3 years Percentage distribution.

	♀ (n=81)	♂ (n=121)	χ^2 test (for sex difference)
a) Hard to understand	2	5	
b) Mostly intelligible	17	32	a + b versus c p = 01
c) No difficulty in understanding	81	63	

The girls can make themselves understood earlier than the boys

The assessments of enunciation at 3 and 5 years made by psychologists in connection with the testing and investigation of the child are shown in Table 9

Table 9 Ratings of enunciation at 3 and 5 years of age
Percentage distribution.

	Enunciation			
	at 3 years		at 5 years	
	♀	♂	♀	♂
Ratings	n=85	n=116	n=80	n=115
1	2	4	0	2
2	15	29	3	7
3	40	44	25	28
4	35	24	64	57
5	7	0	9	6

Sex difference at 3 yrs: enunciation ratings 1-2 vs 3-5 p = 01
at 5 yrs: enunciation ratings 1-3 vs 4-5 n s

Even according to this structured psychological assessment there is a striking difference between the sexes at 3 years significant at the 01 for enunciation defects In the significance test (x^2) rating scores 1 - 2 have been combined in one group and 3 - 5 in the other Since the same clearly defined measure of speech defects has been used at both 3 and 5 years the rising frequency of the ratings denoting better speech capacity reflect the progressive development of speech as the child grows older

The superiority shown by the girls in this sample as regards the early age at which they are able to make themselves understood and the more advanced state of their enunciation is corroborated by many other studies (see Mc Carthy 1953) In the corresponding longitudinal study in London Terence Moore has found in a comprehensive study of speech development that at 18 months though not at ages subsequently investigated (3 years 5 years and 8 years) the girls had advanced further than the boys in terms of speech maturity and vocabulary (6)

Results

The children who at 3 years showed the greatest speech retardation and were classified as hard to understand (2 girls and 6 boys) still had certain difficulties (5 out of 8) in making themselves understood at the age of 5 years One of them spoke quite correctly for its age while the others exhibited various specified consonant defects When they started school two years later infantile speech with poor enunciation and/or difficulties with particular sounds were still present in half the 8 children originally noted as speech-retarded.

Fig 1 shows the development of these considerably speech-retarded children (group a in Table 8 page 150) and the relatively inarticulate children (group b) during the pre-school years with regard to enunciation defects Although the percentage frequencies are different among boys and girls the shape of the curves is similar and the children have therefore been combined in a single group The continuous curve thus represents the diminishing trend of the frequency for the entire sample The difference between the curve and the cross-section values represented by the bars denotes the number of additional enunciation defects existing in the children in the sample at different ages

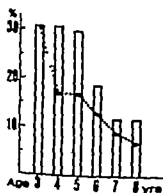


Fig 1. Frequency of children with speech retardation and enunciation defects Percentage distribution. Curve = longitudinal values
Bars = cross-sectional frequency

THE CO-VARIATION OF SPEECH RETARDATION AND BEHAVIOURAL VARIABLES

Results

Children with moderately and severely retarded speech development at 3 years do not differ significantly from the other children in the sample as regards certain motoric skills (walking without support at or after 12 months) (X^2 = 0 372)

Nor can any difference be established as regards the frequency of temper tantrums at 3 years (X^2 = 0 025)

Children with retarded speech development are relatively more prevalent among those reported as being more destructive than others but the X^2 value is not significant (X^2 = 2 531) Similarly it is relatively more common for speech retardation to be found in children with less well-educated mothers but this distribution too may be coincidental (X^2 = 2 238)

If children from families with different reading habits (= reading aloud to the children) are compared with one another against the background of the speech retardation variable the following emerges Of 59 children with speech retardation at 3 years only 23 were reported by their mothers at the 2-year investigation to have had experience of habitual reading (information is lacking for 2 children) The corresponding figures for children whose mothers had not observed any notable speech retardation were 79 out of 137 (X^2 = 4 755 p = 05) Children who from an early stage had listened to this kind of entertainment and obtained more extensive language practice through being read to also occurred less frequently in the speech-retarded group

CO-VARIATION OF ENUNCIATION DEFECTS AND THUMB-SUCKING

A previous study of habitual thumb-sucking (page 50) established a statistical connection (p = 025) between prolonged thumb-sucking and lisping between the ages of 4 - 5 years This connection becomes more apparent if enunciation defects are taken to include other consonant difficulties as well as those concerning fricatives (X^2 = 7 644 p = 01) A summary of the frequencies in the fourfold table is given

Table 10 Consonant enunciation defects and prolonged thumb-sucking

	Consonant enunciation defects at 4-5 years (n=40)	No such defects (n=164)
Prolonged thumb-sucking	20	45
Others	20	119

DISCUSSION

The speech of many children is clearly incomplete at 3 years Even when they start school about one-quarter of those classed as retarded at 3 years still pronounce certain sounds incorrectly These enunciation defects are not serious but they are relatively persistent The most frequent deviation is an incorrect enunciation of fricatives Since the frequencies quoted for the ages of 6 - 8 years are based on the mothers opinions they presumably represent a minimum.

It is worth pointing out in this connection that parents who are in the habit of reading aloud to their children during the speech development period have relatively fewer children with retarded speech. This suggests that daily listening practice with a wider range of language provides the training and stimulus needed for adequate speech. This method of reading aloud to prepare speech development is probably the simplest most natural and from the children s point of view the most enjoyable way of rapidly achieving correct speech. The stimulus is probably of great value regardless of the hereditary element by which speech development is also influenced.

The supposition that children who cannot make themselves properly understood are more prone to temper tantrums or destructiveness than others at this early age (3 years) is not verified by this material Of course this is not to say that the observation is groundless Temper tantrums are among children of this age only too common a way of

in terms of pronunciation. The most advanced children still retain a considerable lead at 8 years

DISCUSSION

The differences in Terman-Merrill quotients between the groups at 3 years are not surprising as regards either enunciation or speech maturity Regardless of whether speech imperfections are an expression of low general ability or a specific speech retardation, the construction of the test leads one to expect these differences Tests of a child with an impaired speech function should always be supplemented by a non-linguistic test But the slight equalization that has occurred between the groups by 8 years suggests either that the element of children of low general ability is particularly dominant among 3-year-olds with enunciation defects or that the consequences of the language handicap are slow to disappear At all events, these children who are speech-retarded at 3 years run the risk of starting school with an obvious handicap and with less chance of assimilating the instruction they receive Insofar as language training combined with other intellectual and emotional stimuli is successful this particular risk group should be given priority for early admission to nursery school

Summary

The speech of a randomly recruited sample originally numbering 212 children studied longitudinally up to the age of 8 years has been investigated as regards disturbances in speech flow and enunciation defects

I. The first of these are more common even in their milder and more temporary forms in boys than in girls The sex difference between the cross-sectional frequencies is clearly statistically significant between 5 - 7 years Stammering" in pre-school children is often of a clearly episodic character Temporary disturbances predominate at each annual investigation. 20 % of the disturbances first appearing at 3 4 or 5 years reappear only once during the observation period up to 8 years Many of the speech defects reported by mothers below 3 and 4 years are presumably due to speech not yet having attained sufficient stability and firmness of organization so that it is relatively easily disturbed by environmental influences during the development phase

A definite chronological connection with accidents or other defined frightening experiences was found in 11 of the 66 cases exhibiting non-fluency in speech between 3 - 5 years Apart from these presumably causal connections significance testing did not establish any tendency to stammering on the part of others who had been involved in accidents or other frightening experiences Speech disturbances appearing in connection with a dramatic experience were neither more nor less persistent than those which began less conspicuously

Significant co-variation was established with the variable coercion during toilet training which the author is disposed to interpret as an indication of a speech defect generated by conflict tension. Speech reactions were also accompanied to statistically significant extent by poor appetite tics and masturbation all of which were interpreted as simultaneous reactions in different behavioural variables to emotional tension. No connection could be established with weaning troubles thumb-sucking nail-biting sleep disturbances night wetting or encopresis shyness or temper tantrums nor with social class status the mother's education or marital status (at the

time of the child's birth), nor with the birth of a sibling.

II Enunciation defects occur as a sign of retarded speech or general development or are acquired without having been noticed previously. At 3 years 2.4 % of the girls and 5 % of the boys speak in a way which even close relatives have difficulty in understanding. Enunciation and speech maturity assessed by a psychologist at 3 and 5 years on the basis of a 5-point scale reveal a significant ($p = .01$) sex difference at 3 years but not at 5 years.

A description is given of the persistence of enunciation defects up to the age of 8 years. Half the children who were most retarded (unintelligible) at 3 years were still speaking in an infantile manner when they started school, with indistinct enunciation and/or difficulties with particular sounds, the commonest defect being lisping.

Speech retardation was less prevalent in children whose parents were in the habit of reading aloud to them. This test referred to reading aloud noted at 2 years and speech retardation at 3 years. Significance $p = .05$

The following emerged concerning the connection between ability and speech retardation/enunciation defects. The significant ($p = .001$) mean differences which understandably enough were established between children with different degrees of speech retardation and others at 3 years were practically unchanged at 8 years. Standardized Terman-Merrill quotients were used at both ages. Although there are children with so-called specific speech retardation whose measured test results improved considerably between 3 and 8 years, taken as a group 3-year-old children with speech disturbances are worse off than their classmates when they start school. There is a large element of general retardation. The speech-retarded infant should be regarded as a child at risk and should be given priority for development-stimulation in nursery school.

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CHAPTER XIV

F U R T H E R S T U D I E S O F S L E E P B E H A V I O U R I N A L O N G I T U D I N A L L Y F O L L O W E D U P S A M P L E

(principal ages for this section 4-8 years)



FURTHER STUDIES OF SLEEP BEHAVIOUR IN A LONGITUDINALLY FOLLOWED UP SAMPLE

(principal ages for this section 4 - 8 years)

INTRODUCTION

Interest in sleep research during the past decade has been primarily of a neuro-physiological nature Refined methods have made it possible to chart the different stages of ordinary sleep Remarkable results have also been obtained concerning sleep disturbances such as somnambulism (2 5) The connection between somnambulism and dream sleep has been disproved by the appearance of the EEG (3 4 8)

The present study is not concerned with the physiological basis of sleep but rather with the way in which that basis is expressed through habits and sleep disturbances Sleep conditions have been observed and reported by the mother It is her experience of events at home during the night that is presented here The report consists of facts concerning sleeping times and sleep disturbances provided by her In many respects the present report is a sequel to the account already given of sleep behaviour up to the age of 3 years. (6) The material has been taken from the same prospective longitudinal study

An account of the wealth of data concerning sleeping habits will be divided up under the following heads: sleeping habits and length of sleep resistance at bedtime night waking and somnambulism. Our main concern will be with conditions between 4 - 8 years though previously published data may also be added to illustrate a tendency in a continuous process Data from the first year of life which have not been published before may also be included in the account because of their relevance to subsequent ages

Method

Data concerning sleep conditions are given at 4 - 5 years in form VI: items 47 - 48 and 6 - 8 years in questionnaire V: items 16 - 23 and form V: items 66 - 69 (sleeping times) At 4 and 5 years the mothers were interviewed by the psychologist following a standardized schedule of questions.A somewhat different questionnaire was

used at *6 - 8 years: this was completed at home and then supplemen-*ted during the visit to the clinic While the questions in the two questionnaires cover very much the same ground they are somewhat differently phrased. Another difference is that whereas personal interviews were a regular practice at the earlier ages they were reduced to a supplementary role later on.

SLEEPING HABITS AND DURATION OF SLEEP RESULTS

Bed time, awaking time and lenght of sleep

During the period under consideration, bedtime becomes progressively later and the number of hours the child sleeps every twenty-four hours gradually decreases. Up to 3 years of age the average sleeping time was reduced above all by the decrease and ultimate disappearance of daytime sleeping the duration of night sleep remaining relatively unaltered. As in the previous study data on sleeping and waking times to the nearest half hour were collected at every visit up to and including 8 years The times specified refer to typical weekday mornings and evenings

No significant differences have emerged between the girls sleeping times and the boys The entire sample has therefore been grouped together in each of the cumulative percentage curves denoting sleeping and waking times at 4 and 7 years (fig 1) These ages have been chosen to represent preschool and early school age Half the 4-year-olds are accustomed to going to bed later than 7 15 p.m. while half the 7-year-olds regularly go to bed after about 8 15 p.m. Differences in the duration of morning sleep tend to cancel out taking the group as a whole

The duration of sleep in an ordinary twenty-four hour period has been calculated on the bases of the sleeping and waking times reported. Some children still have a short sleep during the day at 5 years more specifically 5 % of the sample (= 10 children) as against 13 % at 4 years Three of these children sleep for anything up to 2 hours during the day As in previous investigations hours of sleep during the day and during the night have been added together Means and standard deviations for the entire period from ½ year to 8 years are shown in the graph in fig 2. After 6 years hours of night sleep are the same as hours of sleep per twenty-four

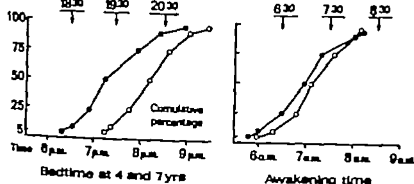


Fig 1 Sleeping and waking times for children at 4 and 7 years respectively

hours. Table 1 shows the numerical values and standard variations of the total duration of sleep per twenty-four hours on which fig 2 is based.

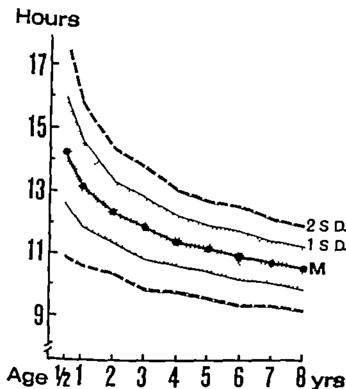


Fig 2. Means and standard deviations for duration of sleep in hours at the ages of ½ – 8 years inclusive

Table 1 Duration of sleep at different ages (means and standard deviations)

Age in years	1	2	3	4	5	6	7
Total length of sleep (night + day)							
Means of hours	12 3	12.4	11 9	11 8	11 6	11 1	10 8
S D	± 1 3	± 1.0	± 1 0	± 0 8	± 0 8	± 0 8	± 0 7

<u>Duration of sleep and season</u>

The correlation of duration of sleep and season i e the number of hours of sunlight per day on the child s birthday has been calculated using the Pearson correlation. Children born during the darker half of the year did not sleep longer at the time of their birthdays than children born during other seasons The correlation coefficient are shown in Table 2.

Table 2 Relation of duration of sleep to season (4 - 8 years of age)

Age in years	4	5	6	7	8
Correlation-coefficients	± 0	- 09	13	- 03	07

The correlations are weak and not significant The same applies to relations to duration of night sleep for which special correlation estimates were made at 4 and 5 years (coefficients - 01 and - 10 respectively)

Correlation between durations of sleep of different ages

Correlations of the same child s duration of sleep in different years yield the correlation coefficients summarized in Table 3 The correlations are far from high, but are at least far better than the relations calculated earlier for ages below 3 years (6)

Table 3 Correlation coefficients of duration of sleep at different ages (Pearson-correlation)

Age (in years)	5	6	7	8
4	32xxx	35xxx	(13)	28xxx
5		34xxx	35xxx	38xxx
6			50xxx	40xxx
7				47xxx

xxx = p 001

Brackets signifies correlation not significantly differing from 0

Sleeping place

The sleeping accommodation provided for a child is very largely dictated by social reality There is often a shortage of space so that many families are unable to give their child or children a separate bedroom for the first few years After a few years when the family has acquired more living space (7) a new child is often added to the family so that even if the parents now have a room of their own, the children generally have to share This process is illustrated in Table 4 by cross-sectional figures for different ages up to 8 years.

Table 4 Sleeping place Percentage distribution

	Age in months 1	6	in years 1	2	3	4	5	6	7	8 yrs
Child sleeps alone	14	12	13 5	9	12	9	12	13	16	13
Child shares bedroom										
with sibs	3	10 5	17	25	35	46	54	55	59	64
with parents	70	63	58	55	42	33	22	32	25	23
other combinations	12	14 5	11	12	11	11	12			

Although practically every child has a bed of its own to sleep in many of them spend a greater or smaller part of the night in one of their parents beds generally the mother s Table 5 gives data showing developments in the sample in cross-sectional figures from 4 to 8 years inclusive The terms often and sometimes used in the questionnaire completed by the mother at 6 - 8 years have been taken to correspond to the more exact specifications of 3 - 6 times/wk" and 1 - 2 times/wk" on which the figures for 4 and 5 years are based

Table 5 Frequency of children sleeping part of the night in the bed of the parents at 4 to 8 years of age Percentage distribution.

	At 4 yrs of age (n=204)	5 yrs (n=198)	6 yrs (n=188)	7 yrs (n=185)	8 yrs (n=189)
1 Every night	18	14	7	6	6
2 3-6/week = often	12	8	15	9	6
3 1-2/week = sometimes"	8	11	14	14	6
1 + 2 + 3	38	33	36	29	18 %

The father s bed is not chosen nearly as often as the object of the children s nocturnal visits though it figures in one of every four visits by the boys and one of every six by the girls and still less frequently after 8 years Figures are only available for ages after 6 years

Adding together the numbers of children who sometimes often or always visit one of their parents beds we find as can be seen from the bottom line of Table 5 that at 6 years they comprise one-third and at 8 years barely one-fifth of the sample

Table 6 Frequency of "night-visitors in parents beds in relation to social groups and gainful employment of the mothers

At 4 years of age (n=204)		to parents bed	no visit or seldom	difference
Swedish social group	1.	13	19	
	2	23	61	χ^2 = 6 188 (2 df)
	3	40	48	p = 05
at 8 years of age (n= 193)	1	6	25	
	2.	10	72	χ^2 = 3 685 (2 df)
	3	18	58	p = n.s.
at 4 years of age:				
M. gainfully employed		23	30	χ^2 = 1 188 (1 df)
no such work		53	98	n.s
at 8 years o. age:				
M. gainfully employed		12	50	
no such work		22	105	χ^2 = negligible

Table 6 shows the number of children in the habit of visiting their parents beds divided according to social class and the mother s gainful employment The Swedish triple classification of social status on an occupational basis has been used here Gainfully employed mothers have been taken to include both full-time and part-time employed. All three levels of frequency of night visiting shown in Table 6 have been included. Since the difference in behaviour between boys and girls is negligible both sexes have been combined in a single table

RESISTANCE AT BEDTIME

40 - 50 % of the children are reported to a greater or lesser degree as being troublesome and unwilling to go to bed when it is time for sleep This applies throughout infancy and has not diminished during the first year at school. Data for Table 7 have been taken from form VI: item 55:8 9 at 4 and 5 years and questionnaire V: item 16:2 - 4 at 6 - 8 years There is no difference between the sexes

Table 7 Children with resistance at bedtime Percentage frequency in cross-sectional sample at 4 5, 6 7 and 8 years of age

	Usually + sometimes
4 yrs	42
5	43
6	40
7	44
8	45

This unwillingness to go to bed is often a characteristic trait which constantly recurs in the investigations of certain children year after year The frequency with which this occurs is shown in fig 3 where the curve denotes longitudinal behaviour The bars give for purposes of comparison the cross-sectional percentages for the corresponding years

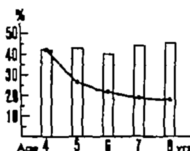


Fig 3 Persistence of resistent behaviour at bedtime

——— = longitudinal percentage curve pure sample

☐ = cross-sectional percentage

DISCUSSION

Obviously going to bed is not quite the attraction to many children that their parents would like it to be and presumably find it themselves If this conflict is reiterated night after night widespread irritation results Often such conflicts can be symptomatic of a more comprehensive and thoroughly strained parent-child relationship. The bare figures provide no indication of this The percentages include both habitual behaviour (termed "usually" or often by the mother) and the less frequently recurring troubles reflected by the term sometimes" At 4 and 5 years approximately half of those putting up resistance do so habitually This category gradually diminishes as the years pass: at 6 years c 1/3 and at 7 and 8 years c 1/4 of all those noted for difficulties at bedtime The data analysed here do not reveal how often the parents expectations in this situation are anachronistically high nor how often the child s resistance is exceptionally easily provoked

Introduction

A high frequency of night waking was demonstrated in the study of sleep behaviour up to the age of 3 years (6) Here we shall examine the development of this situation up to the age of 8 years Cross-sectional figures will be presented for different ages together with subsequent developments in children with manifest sleep disturbances at 4 and 5 years

Definition

Children who have woken up during the night _after_ their parents have gone to bed have been registered for night waking This is an operational definition which takes into account the possible effect of night waking on family relations rather than the point in time at which the disturbance occurs Thus a child waking up at 11 p m. is generally more of a disturbance to a family accustomed to going to bed early than to parents who are still up Similarly early waking in the morning between 5 - 6 a.m. may be perfectly suited to the routine of one family while another may find it irritating and tiring

Method

Night waking was registered in slightly different ways at the interviews during the first five years and in the questionnaire filled up by the mother at home and completed at the clinics at 6 - 8 years of age The first of these gave a more exact description of the frequency and character of night waking and the nature of the countermeasures taken (form VI: 61 - 72) The degrees of frequency were: waking once or several times during the night 3 - 6 nights per week 1 - 2 nights per week less than one night per week and never In the questionnaire completed by the mother (and supplemented at the clinic) the incidence of night waking was graded as follows: always often sometimes seldom and never (V: 21) This difference should be borne in mind when considering the results

FREQUENCY RESULTS

There are no significant differences as regards night waking between boys and girls Both sexes have therefore been combined in a single group for accounting purposes Table 8 shows the percentage distribution of night waking between different frequency levels

Table 8 Incidence of night waking at 4 to 8 years of age
Percentage distribution. Both sexes

Age in years	Nightly	3-6/week	1-2/week	all together
4 (n=204)	23	11	10	44
5 (n=198)	20	10	13	43
	always	often	sometimes	
6 (n=200)	4	10	29	43
7 (n=194)	5	8	23	36
8 (n=196)	4	5	23	32

PERSISTENCE

The cross-sectional figures illustrate the situation in the sample as a whole at different ages but they do not reflect the changes in the behaviour of the same children from year to year Nor do they show how persistent a behaviour is This is done in fig 4 starting with night waking at the age of 4 years

Method

Only children who have attended every investigation (pure sample) are included in the curves which cover disturbances of all three levels of intensity (nightly 3-6/w = often 1-2/w = sometimes) Any variation in behaviour between these three levels over the years has been disregarded. If on the other hand a lower waking frequency than the above has been reported at any of the annual investigations sleeping behaviour has been regarded as normal and

the disturbance as no longer occurring in which case any subsequent disturbance has been counted as episodic and temporary

RESULTS

Thus the curve in fig 4 refers to the percentage of night awakenings that have persisted year after year starting with the figures at 4 years The bars denote the percentage with sleep disturbances (cross-sectional data) in the pure sample at the different ages The percentage differences comprise night wakenings which are either new or have revived after having been in abeyance for a period of time

The curve suggest that nearly a quarter of night-waking 4-year-olds are liable to remain so year after year until at least the age of 8 Similarly one can see that one-third of the families with children waking at the latter age have had long experience of this behaviour

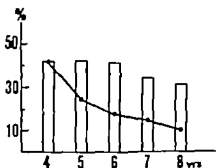


Fig 4 Persistence of night awakening in pure sample
Percentage distribution.

Curve - persistent night awakening
Bars - all night awakenings at respective ages

NIGHT WAKING BEHAVIOUR

The way in which the child behaves when it wakes up during the night can provide an indication of why it wakes up The description given of its condition by the mother has been based on a structured interview Data on the subject are included in the interviews up to and including 5 years (VI: 62: 0-9) In Table 9 an attempt has been made to group the reasons according to the mother s description. The analysis comprises children who have slept badly for a period of more than 6 months between the ages of 3 and 4 years and between 4 and 5 years The percentages are based on the total number of children in the sample

Table 9 Behaviour at awakening in the night at 4 and 5 years of age Percentage distribution, calculated on the whole sample

	At 4 yrs of age (n=204)	at 5 yrs of age (n=198)
Cheerful, just wants attention	20	18
Toilet need	12	11
Upset, frightened	4	3
Miscellaneous	4	3
(Good sleepers)	(60)	(65)

It may be mentioned for the sake of comparison that another 5 % of the children in the sample are noted at 4 years waking up frightened or upset but this has happened only on isolated occasions during the past year to children who are otherwise classified as sound sleepers The corresponding figure at 5 years is 8 %.

Concerning this topic see under headings of discussion page 177

THE CO-VARIATION OF NIGHT WAKING WITH CERTAIN ENVIRONMENTAL VARIABLES AND SPEECH IMPEDIMENTS

The environmental variables tested are (1) the mother s gainful employment (2) the child s separation from the home in a completely strange environment and (3) the child s experience of and reaction to accidents or frightening events

Method

The category of gainfully employed mothers has been made to include all those with some kind of employment at the time of the investigation no matter how regular or irregular Most of those included in the group are regularly employed on a full-time or part-time basis The comparison does not take into account where the child spends its time or who takes care of it while the mother is at work.

Variable no 2 includes the children who are cared for outside the home and by some other person than their mother or a relative not only during the day but also at night These children have been living in another private home in hospital or at a children s home

Variable no 3 comprises children who have been involved in accidents or undergone some other frightening experience

In variables no. 2 and 3 the comparisons have been limited to 4 and 5 years The X^2 analysis regarding the mother s employment extends as far as 8 years.

The prolonged speech impediment variable (tendency to stammer) comprises children who were constantly noted for stammering to a greater or lesser degree between 3 - 8 years

RESULTS

The results are given in Tables 10 and 11

Table 10 Covariation of night waking and certain environmental variables.

	At 4 years	5 years	6 years	7 years	8 years
Mother s gainful employment	05	n.s	n s.	n.s	n.
Child s separation from the mother	10	02			

Of the variables tested it is above all the placing of the child in a strange environment that shows a significant co-variation with night waking (2 % level at 5 years) A similar tendency is noticeable at 4 years but is not significant (χ^2 = 3 026) The occurrence of sleep disturbances was also probably significantly more frequent for children with gainfully employed mothers at 4 years of age but the covariation did not appeared of any other age

Comparing the children in the group for prolonged sleep disturbance with other children with regard to stammering tendencies yields the following distribution.

Table 11 Persistent sleep disturbances vs prolonged speech impediments.

	Bad sleepers 4-6 years	Others	
Prolonged speech impediment	9	19	χ^2 = 4 524
Others	27	145	p = 05

The distribution in the fourfold table shows that prolonged night waking is combined with persistent speech impediments more often than can be attributed by chance

DISCUSSION

The supposition that children habitually waking during the night at 4-5 years mostly show signs of fright is not borne out by the the facts. Nightmares or a fear of the dark that upsets the child are in a minority compared to other causes It is common for children of this age to wake up because they need to go to the toilet but in most cases the reasons are impossible to trace: they wake up merely displaying a need for playful attention. Waking may be connected with physiological variations in the depth of sleep which are

a part of normal sleep behaviour Children at a superficial stage of sleep can probably be woken by such slight disturbances that it is impossible to point to any particular causes The disturbances in question may not a ways be such palpable things as external stimuli physical discomfort or needs or signs of mental imbalance In most cases it is probably sufficient to speak in terms of night waking instead of sleep disturbances if the latter are taken to refer to pathological conditions There are a few more observations which can well be accommodated in such an interpretation. Night waking often recurs persistently month after month. It may be connected with the physiological type of sleep with which the child is equipped The large group of children with night disturbances wake up without being emotionally disturbed contrary to what one would expect if waking were due to mental disturbance

These reflections are not designed to play down the indication which sleep disturbances may provide of environmental influences The established co-variation with prolonged speech impediments should presumably be interpreted as indicating a stress factor in the background as should the fact that children who have had to be separated from their parents and put in a strange environment (another private home a children s home or a hospital) are represented to a large and statistically significant extent among those suffering from sleep disturbances

A small child who wakes up during the night generally wants something from those around it This is still more true during infancy and the following year when children attract attention by crying A child of 4 or 5 on the other hand, is less disposed to cry in order to obtain the security it seeks after waking up during the night As a result its parents suffer less inconvenience even if the child seeks its security in their beds Many mothers in this sample have testified to the furtive and almost inconspicuous way in which their children climb into bed with them. Sometimes the mother does not wake up when the child comes but discovers him in bed with her later in the morning Sleep disturbances in the sense of inconvenience to the family are far less frequent around 4 - 5 years than earlier at the same time as the frequency of night wa-

king is still remarkably high and differs little from previous years. This observation is corroborated by experience of work at child welfare centres A 4 or 5-year-old child is less likely to be accompanied by the exhausted haggard mother so frequently associated with the lively night-waker of twelve months

Parental response to night waking

The most effective means of getting wakeful three-year-olds back to sleep for the rest of the night was found to be to let them sleep with their parents This is still the main resort at 4 and 5 years The next most frequent resort is to attempt to settle the child by talking to it giving it something to drink tucking it in and making a fuss of it A few mothers report that they have punished their children or scolded them but nobody finds this an effective remedy Irritation and anger are less common in the account of remedies tested Waking has been ignored in 3 % of the methods considered effective at 4 years Sedatives seem by all accounts to have been used very seldom. Of the 6 cases reporting their use half considered them to be ineffective Even for those who tested a variety of methods the parental bed was generally the ultimate resort How common this is can be seen from Table 5 on page 166.

INTRODUCTION

Any direct link between dreams and sleepwalking has been considered disproved ever since EEG and EMG investigations were used during the mid-1960s to prove that somnambulism never begins during REM sleep (1 3 4) The old idea of sleepwalking as action due to the influence of dreams is also hard to reconcile with the inability of the sleepwalker to recall any dreams in connection with the event Neuro-physiological discoveries have prompted the question whether sleepwalkers are not more awake than asleep (4 5) It has not been possible to ascertain any reason for the sleepwalker acting as he does. Even if neuro-physiological discoveries have ruled out dreams as the precipitator of this species of coordinated muscular activity the question still remains why somnambulism is commoner in certain mental states than in others (9) The comparatively higher incidence in children as compared to adults is thought to be connected with an organic immaturity factor The statistically significant rise in frequency of sleepwalkers to be found in their parents as children has been presumed to indicate a genetic predisposition for the condition.

The information given by the mothers in this study during regular structured interviews concerning their children s sleep deviations make it possible to test certain statistical relations between variations and deviations in sleep behaviour The material can be suitably applied to the question whether somnambulism co-varies directly with other notable forms of behaviour exhibited by the child in connection with sleep Attention here will above all be devoted to the statistical relations between somnambulism and bad dreams.

Method

Data concerning somnambulism were first collected at 6 years (V: item 23) The answers are graded according to frequency on a five-point scale: never seldom, sometimes often always

Frequencies in the "bad dreams variable at 6 - 8 years of age have been noted on the same five-point scale as somnambulism (no seldom, sometimes often and always) The last of these categories was not used in any of the answers. Mothers were also asked to give examples of dreams

RESULTS

Somnambulism, Frequency, Persistence

Since there is no difference between the sexes girls and boys have been counted together The percentage incidence in cross-sectional investigations at 6 - 8 years is shown by the following table

Table 12. Incidence of sleep-walking at 6 - 8 years of age Percentage distribution. Cross-sectional

Age in years	Seldom	Sometimes	Total
6 (n=200)	5 5	3 5	9
7 (n=192)	4 6	5 2	10
8 (n=194)	6 6	5 6	12

Approximately half the children noted for somnambulism during the three-year observation period 6 - 8 years had been reported as only seldom" suffering from this condition and at no more than one annual investigation. This group numbers 19 children. The remainder (=18) have been noted for the symptom at two or more of the three annual investigations The maximum incidence within this group is represented by 5 children classified sometimes" at all three annual investigations Thus no children walked in their sleep often or always" It is hard to convert these designation into a fixed number of nights per month: the scale reflects the mothers own interpretation of the expressions Fig 5 shows the prespects of a child who walks in its sleep at 6 years continuing to do so during the years immediately following.

All the children (seldom + sometimes) awarded a plus rating are included here Only children investigated every year are represented (pure sample)

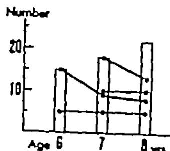


Fig 5. Persistent sleepwalkers (curve) in relation to cross-sectional number(bars).Pure sample

——— = seldom + sometimes

- - - - = sometimes

As can be seen from fig 5 somnambulism also occurs as a sporadic phenomenon for a year or so and then disappears. Persistence during the observation period is more conspicuous when the symptom has appeared more frequently (the broken line in fig 5)

Bad dreaming, Frequency, Persistence

The distribution between different frequencies is shown in the table In the absence of any statistically significant difference between the sexes boys and girls have been counted together

Table 13. Incidence of "bad dreams at 6 - 8 years of age Percentage distribution, Cross-sectional

Age in years	Seldom	Sometimes	Often
6 (n=200)	32 5	18	1
7 (n=192)	37	17	1
8 (n=194)	41	13	0 5

The development and persistence of the symptom in the same individuals during the period 6 - 8 years is illustrated against the background of the cross-sectional figures in fig 6



Fig 6 Persistent bad dreaming" (curves) in relation to cross-sectional number (bars) Percentage distributions Pure sample

Thus according to the mothers reports it is not particularly common for the symptom to remain a prominent feature of the child s dream life for a matter of years It is more temporary than persistent Six-year-olds having nightmares are only troubled by them to a slight observable extent at 8 years

COVARIATION OF SOMNAMBULISM AND BAD DREAMS

The simultaneous occurrence of somnambulism and unpleasant frightening dreams is shown by the following table

Thus somnambulism occurs in the same children together with frightening dreams to a greater extent than can be attributed to chance

Table 14. Simultaneous occurrence of somnambulism and bad dreams at 6 7 and 8 years. X^2 calculated with Yate s coefficient

Somnambulism ("seldom" or "sometimes")		Bad dreams sometimes or often Yes	No	X^2-test	Significance
6	yes	4	14	negligible	-
	no	34	148		
7	yes	8	11	= 6 688	01
	no	26	147		
8	yes	10	14	= 16 320	001
	no	16	154		
Somnambulism sometimes between					
6-8	yes	9	5	= 5 647	02
	no	53	127		

DISCUSSION

The habit of sleepwalking and trouble with unpleasant dreams are often a temporary and episodic phenomenon among the children in this sample If they occur simultaneously to such an extent as to suggest more than coincidence one is moved to seek some kind of connection between them. It is unlikely that mothers interpreted sleepwalking as a nightmare activity because when they quoted examples they did not relate the dreams they described to somnambulism. Probably the same background factor that initiates sleepwalking has on other occasions brought about the frightening contents of the children s dreams This observation agrees well with that reported in our introduction, namely that somnambulism appears to be more common in certain mental states than in others (9) At the same time however it should be remembered that temporary somnambulism, which cannot be regarded as a habit occurs more frequently in "normal than has hitherto been realized.

SUMMARY

An account is given of a follow-up of sleep behaviour between the ages of 4 - 8 years in c 200 randomly selected children in the longitudinal Stockholm study Average sleep durations and their standard deviations are calculated for different ages against the background of sleeping and waking times The correlation between the duration of sleep in the same children at different ages is far better than that between the ages below 3 years but the correlation coefficient does not exceed 50 for any of the ages compared.

Between 10 - 15 % of the children have bedrooms of their own. In c 25 % of the families one or both parents are still sharing a bedroom with the child when the child is 8 years old while below that age the proportion is far higher All the children have a sleeping place of their own but a strikingly large number still spend a certain proportion of the night in their parents beds At 8 years the percentage has fallen to 18 % It is statistically probable that this occurs more frequently in social group 3 The mother s employment status would appear to be immaterial

Reluctance to go to bed is often a characteristic reported in the same children year after year The same applies to night waking. The frequency of troublesome night waking diminishes from year to year A distinction should be made between night waking and sleep disturbances Most children waking in the night (at 4 and 5 years) show no sign of fright but rather a need of playful attention. The majority of cases of night waking are thought to be related to physiological variations in the depth of sleep rather than to mental imbalance The placing of children in strange surroundings covaries with subsequent night waking Persistent night waking and prolonged speech impediments occur simultaneously too often to be attributed to chance A study has been made of the occurrence of somnambulism and unpleasant dreams between the ages of 6 - 8 years. Approximately every tenth child is reported to walk in its sleep occasionally at the age of 7 In cases where the symptom has manifested itself more frequently it has shown a marked tendency to

persist unpleasant frightening dreams do not seem to recur regularly in the same child to any considerable extent but as a symptom they are more frequent than somnambulism. Both symptoms occur simultaneously in one and the same child at the ages of 7 and 8 considerably more often than can be attributed to chance ($p =< 01$ and < 001 respectively)

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CHAPTER XV

T E M P E R   T A N T R U M S   A N D   D E S T R U C T I V E N E S S

TEMPER TANTRUMS AND DESTRUCTIVENESS

INTRODUCTION

The following essay is concerned with the frequency and changeability of these symptoms up to the age of 8 years in a randomly recruited group of children. Since both variables have been used in different contexts in the present study of the symptomatology of children, a simple account of their incidence is called for together with an illustration of their co-variation.

Children often display their despair anger or disappointment expressively and immediately by means of physical action. Outbursts of this kind can take various forms but they are all vehement immediate and patent expressions of frustration due generally to a sudden obstacle a restriction of the child s possibilities of fulfilling its wishes The action is more often than not provoked by the prohibitions or other actions of the person or persons in the child s immediate surroundings but outbursts may also be due to physical impediments or failures in play

What is interpreted as destructiveness during childhood is often a mixture of lack of wisdom, incapacity inquisitiveness and vandalism. It may be difficult to identify the underlying factor Among those however we can probably assume that a conscious desire to destroy becomes relatively more predominant with age In view of the difficulty of demarcating the character of this symptom, the frequency study described below has been confined to data from between 4 and 8 years

Method

The children s propensity for temper tantrums has been described every year (interview form VII item 54 - 57 at 4 - 5 years and questionnaire V item 62 at 6 - 8 years) The multigrade scale of the average frequency of serious outbursts per day or other unit of time makes it possible to differentiate Instances of the character and content of the outbursts are entered on the basis of a standardized interview As can be seen from the following there were many alternatives to choose from: lies on floor, stamps slams doors hits inanimate objects hits peopl about throws things screams bites rigid, thrashing limbs hits hurts self blue in face This exemplification of outbursts of temper given

by the mother made for greater certainty in the evaluation of the symptom.

The graduation used at 1 2 and 3 years (usually sometimes, rarely or no) cannot however be transposed directly into the more differentiated specification of frequency used in subsequent years This is marked in the frequency curve by a break.

Symptom persistence has been calculated for a "pure sample i e excluding children who were absent from any of the investigations Since frequency data at 4 years and subsequently are described in

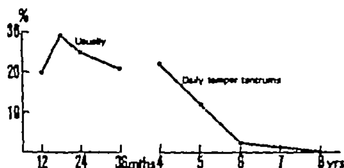


Fig 1 Frequency of children with temper tantrums at various age
Cross-sectional percentage distribution

Frequency of destructiveness

Fig 2 shows the cross-sectional frequencies for different ages (4 - 8 years) Separate curves are drawn as the sex differences proved significant (see below)

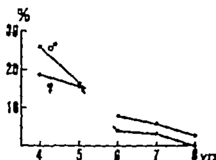


Fig 2 Frequency of children with destructiveness at various ages
At 4 - 5 years: d finite habit
6 - 8 years: often alway
Cross-sectional percentage distribution

As can be seen from the curves boys are considered more active at all ages in pulling things to pieces The frequency differences are statistically significant both at 4 years and at 6 - 8 years (p = .02) For this comparison the destructiveness variable was widened to include children with a moderate habit as well as those with a definite habit

The persistence of temper tantrums

Fig 3 shows how the intensity of daily unrestrained temper tantrums expressed in frequency declines and disappears relatively quickly after the age of 4 years The curve in the lower picture denotes the persistence of the symptom the bar its cross-sectional frequency The upper picture illustrates changes in the degrees of frequency between 4 and 8 years By 8 years the outbursts have either disappeared or become less frequent

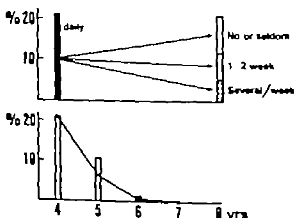


Fig 3 Frequency of daily temper tantrum at various ages

Below: Persistence curve in relation to cross-sectional bars.

Above: Changes in intensity of the habit in children with daily outbursts at 4 years

Percentage distribution in pure sample

The persistence of destructiveness

Corresponding data concerning the persistence of destructiveness are given in fig 4.

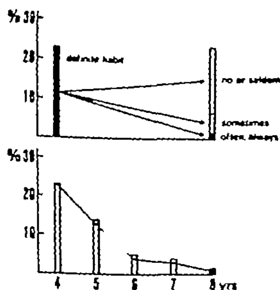


Fig 4. Frequency of destructiveness at 4 - 5 years = definite habit at 6 - 8 years = often always"

Below: Persistence curve in relation to cross-sectional bars.

Above: Changes in intensity of the habit in children with definite habit of destructiveness at 4 years

Percentage distribution in "pure sample

Covariation temper tantrums - destructiveness

The X^2 value for the covariation of daily temper tantrums and definite habit of destructiveness at 4 years is 4.625 (p = 05)
No similar covariation has been established between the less frequent forms of temper tantrums and destructiveness occurring at 8 years.

DISCUSSION

It is obviously very common during early childhood for children to express their feelings by physical activity of the kind termed temper tantrums The tempestuous movements thus generated during the first years of life are not really directed at any particular target The child strikes out, thrashes stamps screams or throws itself into the floor using its entire body to vent its feelings Sometimes adults can establish contact to pacify and comfort the child sometimes they cannot Gradually the outbursts assume a more deliberate and specific character with sudden anger being directed at a particular person or object The boundary between aim-directed destructiveness and uncontrolled bodily activity may disappear By 4 years there exists among the children in the sample a covariation of daily temper tantrums and notation for habitual destructiveness which is probably not just coincidental Although some children are noted for daily temper tantrums unaccompanied by destructiveness it can be difficult for the mother/observer to distinguish between unintentional and deliberate destructiveness

Temper tantrums are a predominantly age-conditioned symptom. Their frequency steadily declines once the 4-year mark has been passed. Children with daily outbursts become increasingly rare None of the children in the "pure 4 - 8 years sample retain the same intense frequency at 8 years In the case of a minority of the children with daily temper tantrums at 4 years the symptom has disappeared entirely by 8 years while 59 % are still liable to react in this way though they do so less often This may be because most children have learned that parents or siblings do not appreciate outbursts and destruction of this sort It may also be connected with an increased tolerance towards the factors provoking the outbursts a tolerance which has developed not only in the child but also in its surroundings It may also be due to a reduction in the number of occasions calculated to produce friction, owing to the considerable periods of time which the 8-year-old spends outside the home However this may be temper tantrums in children of 7 - 8 years would appear to have an altogether more distinctive significance than their counterparts at the ages of 3 - 4 years

SUMMARY

The temper tantrum and destructiveness symptoms are described with regard to frequency sex difference persistence from 4 to 8 years and co-variation. Both symptoms show a steep decline in frequency after the age of 4 years The boys are reported as being more destructive than the girls ($p = < 02$) There is no sex difference as regards temper tantrums There is a certain co-variation between the symptoms at 4 years ($p = < 05$) but no such co-variation can be established at 8 years

CHAPTER XVI

T I C S   I N   S T A T U   N A S C E N D I

T I C S I N S T A T U N A S C E N D I

INTRODUCTION

The tics symptom is generally defined as consisting of rapid involuntary apparently purposeless and frequently repeated jerks in certain functionally co-ordinated muscles or groups of muscles The forms of expression are versatile and varied The most noticeable and perhaps the commonest form of tics involves certain groups of muscles in the face and neck. Blinks with the facial muscles round the eyes nasal and labial movements and grimaces of various kinds turns of the head and shoulder shrugging are thought to be more common than sound tics produced by functional deviations in the passage of air through the larynx palate and nose The commonest pattern of tics over the different parts of the body seems to be such that children with tics symptoms which occur at the greatest relative distance from the face tend to have more tics in nearby groups of muscles too so that in this sense they are more severe

The general fidgeting and exaggerated muscular activity occurring in certain children during childhood (in some cases with definite atato-tic-atactic element due to brain damage) is distinguished by definition from tics by the speed with which a limited group of muscles (as with tics) is stimulated to action. Misinterpretation together with ignorance of the manifestations of the hyperkinetic syndrome during infancy can sometimes lead to a confusion of the two

A prospective longitudinal study is especially calculated to draw attention even to minor forms of deviation Often a phenomenon will start with slight symptoms which are practically indistinguishable from normal behaviour later appearing and perhaps becoming set in a manifestly more substantial symptom of deviation Consequently if certain observations are continually registered and ventually assume the form of a well-defined symptom, it should be possibl to evaluate early symptoms according to subsequent discoveries

The present essy i concerned with the occurrence of tic-like symptoms up to the age of ight years and with the persi tence and deve-

lopment of the symptom Finally we shall consider whether there are any clear links between tics and other symptoms of emotional tension.

RETROSPECT OF EARLIER INVESTIGATIONS RELEVANT TO THIS STUDY

Doubts have been expressed as to whether tics can be diagnosed as early as the pre-school stage Seven years has been specified as the minimum age limit Tic-like muscular movements at earlier ages are regarded as an undifferentiated nervous habit in a child with considerable motor unrest In his textbook of child psychiatry Kanner (10) states that the youngest child with tics observed by him was six years old. A rise in frequency during school age up to 11 - 12 years is regarded as typical of the symptom being succeeded by an appreciable decline in frequency Other writers have described typical tic symptoms in pre-school children (5 6 11) Another view is that tics attain their maximum frequency at the ages of 6 - 8 years (2 14) Between 70 - 90 % of clinical cases can be traced back beyond 10 years (14 11) Prevalence is indicated with a considerable variation ranging from 4 5 % in 10 to 11-year-old boys and 2 6 % in girls of the same age (8) to 23 % of schoolchildren without any further specification of age (1)

According to Kanner tics are a symptom of emotional tension which always occurs in combination with other behavioural deviations a rule to which no exceptions are known A happy secure child never develops tics Mahler (11) interprets tics as an incipient neurosis or as part of the symptoms and the visible expression of an established psychoneurosis She also advocates a distinction between these forms and the state of seve e tics in which the symptom it self represents the central and essential disturbance a psychosomatic disease of the mot ric system (maladie des tics) Other psychoanalysts have put forward the opinion that the symptom constitutes a masturbation equivalent (4 12) In other quarters the cause has been defined as organic in the form of damage to the striopallidal system resulti g from encephalitis or some other form of brain damage (7 13) Some psychologists have espoused the theory that tics are an established conditioned reaction that can be eliminated by negative reinforcement

Clearly the tics symptom has given rise to a wide variety of interpretations Authors writing from the point of view of depth psychology and describing the treatment of individual adult patients find the symptom deeply rooted and difficult to treat (4) A similar attitude can to a greater or lesser degree be discerned among those who have worked with children (11) Although the symptom can disappear quite independently of treatment (16) it can also return to a certain extent after some months or years as a characteristic selected symptom of emotional release in the individual concerned In a follow-up investigation of 220 Danish children on average 9 years afterwards 50 % of the cases were found to be cured i e without symptoms for at least a year (14) The prognosis was worst in cases where a close relative exhibited the symptom simultaneously In a Swedish clinical follow-up investigation of 29 tiqueur children in 1963 two-thirds were found to be free from symptoms (9) The same results were reported from a German investigation as early as 1930 (2) The latest contribution (3) (1969) a follow-up investigation of 89 tiqueurs emphasizes that a long period of observation should be allowed to elapse before giving the proportion of recoveries In this investigation too two-thirds of the cases had completely recovered from the symptom The observation period amounted to 8 years or more

THE FREQUENCY PERSISTENCE AND NATURE OF TICS

Method

Assessment of the occurrence of the tics symptom in the children in this study is primarily based on interview statements (form VI item 20: 0 - 9 at the ages of 2 - 5 years and questionnaire V: item 57: 0 - 4 at the ages of 6 - 8 years) The question put to the mother when the child was investigated between the ages of 2 - 5 years was worded as follows: Have you seen any blinkings jerks or grimaces? This was rephrased slightly for the interviews made between the ages of 6 8 years: Have you seen any jerks blinkings ti or other nervous" movements? Apart from typical tics as defined before only such habitual and sudden muscular activity as has been considered involuntary has been included. This limitation in evaluating the answers applies first and foremost to the conditions referred to as grimaces Whether grimaces are apparently spontaneous or constitute an involuntary individually developed response reaction to definite emotional experience the boundary between them and the classical forms of tics is unstable The check has in most cases been supplemented by a description of the ituations in which the reaction mostly occurred during the ages of 2 - 5 years This has made it possible to assess the child s emotional involvement

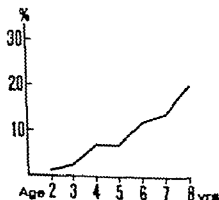
hould however be noted when evaluating the results that the inction posed by given definitions of tics between definite s and nervous jerks of a more undifferentiated variety is unin with regard to children aged 6 – 8 years owing to the lier descriptions of symptoms noted for these ages

: variables included in the interview with the mother and used ied light on the tics symptom are motor unrest temper tantrums ch impediments somnambulism and masturbation. The content of s variables will be described as they are utilized

lts

of the children mentioned below as tics cases has exhibited ulogical brain damage in the simultaneous pediatric investiga-
t

youngest child in whom unmistakeable eye tics were recorded was rears old It had been troubled with blinking for several months symptom disappeared for several years but returned with renewed ength several times daily at the age of six to a somewhat lesser ent at 7 years and sporadically at 8 Another child investigated the age of 2 had been troubled by involuntary nasal spasms and nking for the preceding 3 months



g 1 The frequency of tic-like symptoms at different ages
Percentage distribution

g 1 shows the percentage frequency at different ages from 3 to 8 ars It should be noted that to begin with the symptom appeared

only temporarily i e for short periods sometimes never recurring during the observation period up to eight years It should also be emphasized that the tic-like symptom is generally mild thus differing from clinical cases In the great majority of cases it consists of symptoms from the region of the eye

Table 1 shows how intermittently the "nervous jerks occurred.

Table 1 The intermittent occurrence of the symptom.

Reported at one annual investigation	35 cases
Reported at two annual investigations	18
three	8
four	4
" five	2
six "	1

The symptom occurred between the ages of 7 - 8 years in rather less than half the children who exhibited it for only part of a single year To obtain a better picture and perspective of the figures in the above table which exaggerate the intermittent nature of the tics symptom, one must venture outside the period covered by this essay to trace the occurrence of the symptom at later ages in people whose first period occurred between 7 - 8 years. School age is generally regarded (see Kanner) as the period during which the symptom most frequently appears A comprehensive account of this period will not be possible until all the children have passed the appropriate age A preliminary follow-up of the children whose nervous tics began at 7 and 8 years shows that most of them also exhibited the symptom later on during their school years.

The difference between the sexes is significant at the 5 % level if all the children exhibiting symptoms at one time or another during the observation period up to 8 years are included. The boys predominate This agrees with results obtained in a number of their quarters (5 11 14)

The tic-like movements exhibited by the children in the sample up to the age of 8 years have mainly consisted of blinkings of the eyelids alone or in combination with contractions of the outer muscles of the eyes Nose twitchings persistent and unnecessary clearing of the throat and shoulder shrugging are also represented in the group If the tic symptom returns after having disappeared for a time it tends to assume the same form as on the previous occasion. When the symptom persists year after year as happened in some cases its basis is extended to include additional groups of muscles An example of this is provided by a girl who had eye tics at 3 years 4 years and 5 years At 6 years she was reported as having shoulder shruggings, head turnings and throat clearing as well as blinking A boy with blinikngs continued later on with nose twitchings and lip-licking

DISCUSSION

The main impression on examining the longitudinal symptom chart of the different tiqueur children is that in the majority of cases the symptom occurs during limited periods which are sometimes separated by one or more years without symptoms What ultimately sets in the form of an occasionally mystifying habit has been demonstrated less prominently and expressively during the child s pre-school years as a reaction tendency of the same kind. It is also typical of the pattern that of the relatively large group of children with sporadic symptoms only a minority ultimately develop a condition that could be termed neurotic As long as the symptom is mild and reversible - as it is in the majority of pre-school cases - it should be regarded as a reactive stress symptom. Prognosis and symptom development are dependent on the intensity of the environmental factor to which the symptom constitutes a reaction. Only a very few children in this sample have retained the symptom uninterruptedly during the observation period from the appearance of the very first signs up to the age of eight years Even in these children the frequency-intensity is reported as varying during the period between the annual investigations

The symptom is sometimes stated to have begun in connection with a specified emotional reaction later recurring habitually and without any clear relation to any particular known experience The context

leads one to suspect that what began as a shielding or evasive movement has since become automatic Thus according to the psycho-dynamic view the muscular emotional reaction serves a definite initial purpose If the motivation is removed, the symptom will disappear more easily when it occurs during the period of development preceding the creation of a super-ego This might explain the episodic and sporadic nature of the symptom during early childhood The phenomenon disappears relatively easily at these ages and is incorporated in the pattern of reactions and fixed in automatism if the environmental pressure continues up to an age when the super-ego takes over and consolidates the reaction

Since data on which an interpretation of the origin of the symptom can be based have not been systematically sought in this statistically oriented study the above reflections are based on individual cases. The case histories of psychoanalytical literature describe several children of school age who have exhibited fairly acute tics of various kinds in connection with severe emotional stress (6 12) In these cases the experiences chronologically related to the appearance of the symptom imply that the remaining tic symptom originally has an expressive content

THE RELEVANCE OF EMOTIONAL FACTORS

INTRODUCTION

Most of the cases of tics occurring in adult life originated during childhood A child employs muscular movements to express its feelings and impulses in a far more immediate and obvious way than adults Affect motility or general motor unrest is often a direct reflection of a feeling of pleasure or displeasure excitement anxiety or aggression. The relative sub-cortical domination of motility during infancy is gradually superseded by the deliberately controlled cortico-pyramidal part of the central nervous system. The pressure put on the child by its environment to curb its muscular unrest leads the child to try to suppress it The conflict resulting from the discrepancy between the need for affect motility and the sanctioned means of expressing emotion paves the way for the development of tics

Deliberate control is connected with the development of the ego and its functions of bodily control When eventually the super-ego assumes most of the role of the environment (for which read the parents) the symbolic movement will unless equilibrium has been achieved in the meantime deepen into a neurotic symptom instead of the less persistent reactive symptom it originally was

Mahler (12) has particularly stressed the connection between the child s unrest and other motor expressions of affect on the one hand and tics on the other According to her in the behaviour of children with tics it should therefore be possible prior to the appearance of the symptom to trace definite symptoms of the inability of the ego to control the emotions It is not unusual for the case history of a schoolchild irrespective of the psychic difficulties concerned to include records of earlier outbursts of rage Temper tantrums are far too frequent at 2 - 3 years to be particularly distinctive The symptom must therefore be graded and this is not easily done post facto

The present longitudinal sample affords a certain opportunity of testing the main lines of Mahler s hypothesis (by statistical compa-

rison) concerning the relation between the early incidence of motor unrest exceptional liveliness and poor control of the emotions on the one hand and the subsequent appearance of tic-like symptoms on the other

Method and material

The evaluations and observations compared in the tests of statistical significance concern the extent to which the extreme cases of muscular unrest between 3 - 5 years are relatively more represented in children with muscular twitches and grimaces at 6 - 8 years than among the other children in the sample of the same age Each annual interview includes data concerning whether mothers found their children calm or lively (form VII item 75) At 3 years the graduation is as follows: restless lively medium calm while at 4 and 5 years it is: restless lively quite lively medium, fairly calm and calm. There is no uniform objective scale for symptom evaluation of this kind but the data ought nonetheless to reflect genuine differences in the behaviour of the children in the extreme groups. It is unlikely that the majority of children at one end of the distribution curve would have been placed at the other extreme by another judge Thus the data were collected on average three years before observations of nervous jerks were reported The jerks occurring at the latter juncture and confined to certain groups of muscles are markedly different from general muscular unrest

Children described as restless at some stage during the observation period 3 - 5 years have been placed in one comparative group A tentative examination was first made of the result of a comparison with the other extreme group referred to as calm. The other variable consisted of children who had had tic symptoms at some point between the ages of 6 - 8 years Frequency was not considered in the tics variable the comparison being concerned with the presence or absence of symptoms

Results

9 girls and 15 boys were lassed as restles in one of the three annual investigations at 3 4 or 5 years The corresponding numbers of calm children were 18 and 27 respectively Between these extremes came the other children with various degrees of slight restlessness and qualified calm. On an average of three years later tics symptoms occurred more frequently in the restless children than in the calm ones In a X^2 estimate the difference for both sexes taken together was ignificant at the 5 % level

After this tentative preliminary comparison an stimate was made using the entire sample The restless children were related to the rest with regard to the occurrence of tics Here too it was found

that the group of children noted at an early age as being particularly restless were more prone to develop tic symptoms subsequently than the other children (χ^2 = 6 923)

If the group of 4 and 5-year-olds with a propensity for outbursts of temper is compared with the other children of the same ages regarding the subsequent occurrence of tics between 6 – 8 years no probable significance is obtained for the existence of any difference The χ^2 values are negligible for both boys and girls The same negative result is obtained when children with exceptional outbursts of anger between 6 – 8 years are taken as a comparison group instead of the 4 – 5-year-old temper tantrum children. Not even these children have tics any more frequently than other 6 – 8-year-old who are able to control their tempers

15 girls and 16 boys have exhibited a persistent tendency to temper tantrums between the ages of 4 – 7 years i e they have been noted for recurrent outbursts of exceptional vehemence during these years There is no demonstrable relation in these groups to the occurrence of tics at 4 – 8 years

DISCUSSION

As we have seen the somatic investigation revealed nothing to suggest cerebral neurological damage in children exhibiting tics symptoms between 6 8 years of age The general restlessness exhibited by a large number of them between the ages of 3 and 5 years is therefore assumed to express an emotionally initiated stress factor This is interpreted as a disturbance in the child s equilibrium regardless of whether it is a constitutional weakness individual predilection or unusually strenuous experiences of environment that produce the increase in motility Episodes of manifest tension limited to certain groups of muscles are more likely to follow a year or more later in this group than in the group of more calmly behaved children. This is the relation whose probability it has been possible to establish There are also six to eight-year old children with tic symptoms whose parents have always found them motorically calm and whose tic symptoms have developed so discreetly that they have not been preceded by any visible outward motility disturbances One

might perhaps venture to simplify the equation by surmising that the general "muscular language of the younger child provides an indication of greater risks of changing into an involuntary attitude language in the older child when movement is restricted and inhibitions develop

At the same time one finds no demonstrable frequency correlation between outbursts of the temper tantrum type and contemporary or subsequent tic symptoms The theory which might be based upon this observation is that both temper tantrums and tics provide substitute outlets for increased emotional tension.

CO-VARIATION WITH OTHER VARIABLES

INTRODUCTION

If the tics symptom is regarded as a symptom of emotional tension there may exist co-variation with other expressions of manifest reactive psychic or neurotic symptoms which include motoric elements Somnambulism stammering and nail biting have been chosen as examples of such behaviour This does not imply the precipitate assumption on the author s part that the individual s choice of reaction to stress should primarily be based on such simple rules that reactions with motoric elements accompany one another The choice of these symptoms for purposes of comparison has among other things been due to the fact that psychic conditions such as somnambulism speech impediments and nail biting need not raise questions of interpretation as to whether these phenomena exist or not The habit of playing with the genitals has also been related to the tic symptom.

Method

Observations concerning somnambulism its occurrence and frequency have been described in the essay on sleep and sleeping habits in children aged between 4 - 8 years Systematic collection of data on children suffering from nocturnal restlessness with elements of somnambulism were first collected at the age of 6 years All the children exhibiting this symptom between 6 - 8 years regardl of its frequency (which was generally low) have been included in one comparative group the other group comprising children who have never suffered from this kind of nocturnal restlessness The occurrence of tics in both groups at corresponding ages has been tested for significance (the item numbers for variables of somnambulism are V:23: 0-4 at 6 - 8 years)

as regards the nail biting variable all the children exhibiting the symptom between 6-8 years as well as the children belonging to the group of habitual and persistent nailbiting have been compared in two separate tests with the symptom-free children for the occurrence of tics (item numbers V:33: 0-4 at 6-8 years) The composition of the group of habitual nail-biters is described in the report on nail biting

The stammering variable has been studied and described in the essay on speech impediments The impediments involved are generally slight ones such as stammering (items V:46: 0-4 at 6-8 years)

Playing with the genitals is a common phenomenon particularly among boys The children who have indulged most conspicuously and frequently in this activity have been selected for study as a comparative group Since for natural reasons this habit is more common among boys than among girls the division has been made on a different basis The degrees of frequency given in form V: 36 ranged from 0-4 (= never 1 = seldom 2 = sometimes 3 = once or twice daily and 4 = several times daily) The boys marked 2 3 or 4 in at least two of the annual investigations between 6-8 years formed one group while the remaining children formed the other In order to obtain a sufficiently large girls group all those who at some time during these 3 years (6-8 years) have been marked 2 have been separated from the others At this age none of the girls exhibited any noticeable daily interest in her genitals

Results

The significance tests of co-variation have been collated for the sake of simplicity in Table 2

DISCUSSION

The results are very much as expected. The non-fluency in speech appears primarily in conditions of emotional stress The manifestations of tics are also aggravated in nervous and tense situations It is to be assumed that the same ingredient of emotional tension is present in both symptoms During the observation period 6-8 years the symptoms appear in one and the same individual sufficiently often not to be dismissed as mere coincidence But the question remains why the choice of symptoms sometimes affects the speech and sometimes the contact furnished by the body language

Little is known concerning the deepest causes of somnambulism. This co-variation may indicate that it is a reaction to the same emotional disturbances as give rise to tics

Table 2 The co-variation of the tic symptom with other variables

Variable		χ^2		p
Tics/stammering at 6-8 years	♀	6 163		02
	♂	7 504		005
	♀ + ♂	14 450		001
Tics/somnambulism at 6-8 years	♀	0 417	(yates corr)	-
	♂	4 647		05
	♀ + ♂	5 157		025
Tics/nail biting at 6-8 years	♀	negligible		-
	♂			-
	♀ + ♂	1 616		-
Tics/"masturbation at 6-8 years	♀	12.427		001
	♂	negligible		-
	♀ + ♂	4 948		05

It is not surprising that no demonstrable relation is revealed to the nail biting symptom which is probably of a different etiological nature Nail biting is probably more closely related to defence reactions than tics which contain a larger element of anxiety and fear

It is difficult to explain why there is a definitely significant co-variation with genital play among girls but not among boys Possibly boys with habitual or compulsive behaviour were not sifted out closely enough to distinguish them from the rest The borderline between habits of a greater or lesser degree of compulsiveness is vague in both sexes but it may be that attitudes to this behaviour vary according to whether the child concerned is a girl or a boy If girls frequently play with and probe the vulva tract their behaviour attract more attention and perhaps greater disapproval Those who nonetheless persist at the age in question may be assumed to demonstrate a greater element of compulsion than the others

SUMMARY

Tics or tic-like symptoms in children in a longitudinal growth study have been described with regard to frequency and persistence up to the age of 8 years The tic symptom is more common in boys than in girls In the ages studied it mostly occurs episodically but there are cases where it can be demonstrated to be permanent from the age of 2 years Tics occur most frequently in the region of the eye to begin with When the symptom has persisted for some time it can extend to other functionally co-ordinated groups of muscles

The relation of the tic symptom to motor unrest due to emotional causes and to temper tantrums has been studied A significance test has been carried out to ascertain whether children exhibiting these symptoms between 3-5 years tend more than others to develop tic symptoms between 6-8 years It appears probably (p = 05) that younger children with motor unrest are more liable to develop tic symptoms a few years later than children reported as being of a calm disposition On the other hand it cannot be established that children with temper tantrums are more prone than others to react with a tic symptom.

The co-variation of the tic symptom with stammering and somnambulism in the ages of 6-8 years is significant at least at the 2 % level There is also a strong co-variation in girls who at this age indulge in play with their genitals more conspicuously than other children The same cannot be established for the boys Nail biting does not display any relation to tics

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CHAPTER XVII

S Y M P T O M   C H A N G E S   A N D   S Y M P T O M   L O A D

SYMPTOM CHANGES AND SYMPTOM LOAD

INTRODUCTION

A longitudinal study provides unique opportunities of following a variable flora of symptoms in the individual child over the years The limited task undertaken in the present study has been mainly concerned with the development of certain conspicuous symptoms which are easily observed by the mother It is the occurrence of symptoms of this kind in a normal child sample and the changes which they undergo as the children grow up that I have set out to describe

The first part of this essay deals with symptom changes The latter part with symptom load Previous chapters have described the persistence of various behavioural and developmental characteristics Changes in the longitudinally studied pure sample have been related to changes in cross-sectional figures The estimated percentage differences express the stability of the symptom.

The systematic review now in progress of practically all 4-year-old children in Sweden will presumably lead to the presentation of various statistical series concerning the children s physical and mental health. We should therefore try to analyse the implications of these figures before deciding whether they are satisfactory or disturbing Our assessment must allow for the extent to which the symptoms are transient or persistent

Method

The number of individuals represented in the diagrams below comprise a pure sample i e the diagrams reflect changes in children who attended every interview in the period 4-8 years. The only exception concerns a few children who have been included despit the fact that they were away for one of the five investigations in question. In these few cases the observation period has been 2 years instead of 1 year The pure sample numbers 198 cases

The diagrams depict (a) changes in cross-sectional frequenci s (b) persistence and (c) frequency of recurrences The linear graphs have been drawn to a logarithmic scale in order to bring out the mutual relative changes in frequency The number of case with the symptom in question at the age of 4 is shown on the left and the number at 8 years on the right Since the percentages refer consistently to the same number of children (198) the absolut and the persentage relationships shown by the right-hand scale corre pond to one another The lope of the line indicates a falling or a rising trend. Parall l line regardless of

their level denote the same relative change in symptom frequencies between 4 and 8 years

Cross-sectional frequencies at the different ages are given in Fig 1 while Fig 2-4 shows both the degree of persistence and the frequency of recurrences A persistent symptom is one that has been noted at each of the five investigations between 4 and 8 years; the frequency of recurrence denotes the number of cases in which the symptom reappeared at 8 years after it had been absent at one or several of the investigations between 4 and 8 years The triangular field between the graphs for persistence and recurrence provides some indication of the instability of the variable in question The data have been presented in separate figures purely for the sake of clarity

The frequency graduations of the variables used for these comparisons are those described most fully in the sections dealing with the various symptoms Estimates concerning non-nutritional sucking nailbiting tics and destructiveness are based on the established definite habit Two frequency gradings have been used for temper tantrums that in which the symptom is said to occur at least once a week and that in which it occurs daily Night waking has been included as symptomatic behaviour if it occurs at least once a week To be included in the estimate incomplete bladder and bowel control had to have been current at the time of the interview or to have occurred periodically during the observation year

Results

Falling and rising trends in the occurrence of symptoms in the pure cross sectional sample at 4 and 8 years are illustrated in fig 1 The relative weight of the symptom variable is indicated by its position on the y-axis The divergence between curves reflects differences in the changes - the greater the divergence the greater the change between 4 and 8 years

Figs 2-4 provide some indication of the stability of the symptoms in terms of the relationship between their persistence and their tendency to recur For some of the variables the number of children who had the symptom at 4 years is quite small and the estimated figures should be interpreted with this in mind See figs on next pages

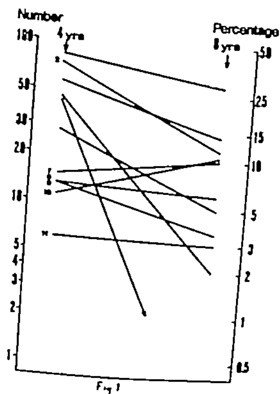

Number
100
50
30
20
10
5
4
3
2
1
4 yrs
Percentage
8 yrs
50
25
15
10
5
3
2
1
0.5

Fig 1

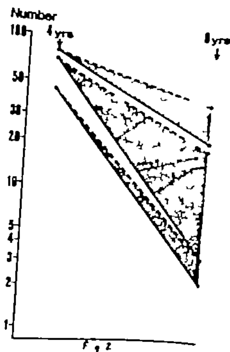

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Fig 2

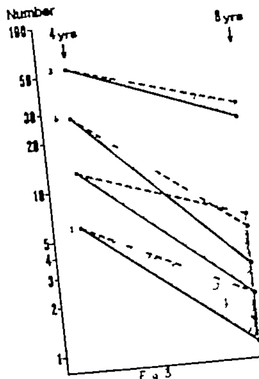

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Fig 3

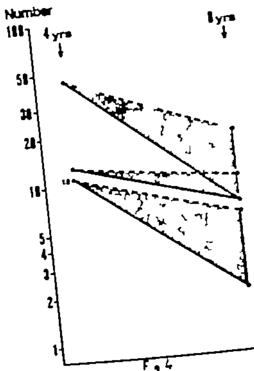

Number
100
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30
20
10
5
4
3
2
1
4 yrs
8 yrs

Fig 4

Fig 1 Changes in cross-sectional frequencies between 4 and 8 years
Pure sample Logarithmic scale

1 = night-awakening (weekly or more)
2 = temper tantrum (daily + several/week)
3 = non-nutritional sucking (def habit)
4 = destructiveness (def habit)
5 = temper (daily)
6 = night-wetting (nightly + periodically)
7 = stuttering (def habit)
8 = nailbiting ( )
9 = day-wetting (daily + periodically)
10 = tics (def habit)
11 = soiling (daily + periodically)

Fig 2. Changes in symptom frequencies of night-awakening (1) temper (
destructiveness (4), Pure sample Logarithmic scale

•———• = persistent number

•– – – –• = recurrent

Fig 3 Changes in symptom frequencies of non-nutritional sucking (3)
night-wetting (6) day-wetting (9) soiling (11)

•———• = persistent number

•– – – –• = recurrent

Fig 4 Changes in symptom frequencies of disturbances in speech-flow (all grades) (7) nailbiting (8) tics (10)

•———• = persistent number

•– – – –• = recurrent

DISCUSSION

The analysis in this report is confined to ten symptom which can easily be observed by those around the child and whose degree and frequency dould therefore be reported fairly reliably

Most of the symptoms described decline in frequency during the period (fig 1) Concern over the child s adjustment generally seems more pronounced at 4 years than after it has started school In several of the variables a proportion of the frequency comes from retarded or strikingly slow maturity: it is the tempo of development that deviates In these variables the symptoms at 4 years are a mixture of retarded development characteristics and secondary symptoms the latter consisting in a relapse into behaviour which is natural at an earlier age and does not differ from that which has occurred all the time This category includes deviations in the functional maturity of bladder and bowels temper tantrums destructiveness and perhaps non-nutritional sucking as well The steepest decline during the period is registered for daily outbursts of temper tantrums (see fig 1) and the habit of destructiveness In contrast to these symptoms there are those which do not occur until a later stage and which are still on the increase at 8 years These include tics nailbiting and to some extent stammering tendencies There is reason to suppose that these symptoms to a greater extent than the former category are expressive of emotional disturbances

As already noted, some problems are mainly age-conditioned so that they are widespread at certain ages By the time this stage has been passed they have lost a great deal of their intensity Development can be rapid and the picture may change within a few years It is hazardous to attach too much importance to the individual child s symptom for purposes of prediction but among all the children exhibiting symptoms of this kind there may be some in whom the symptom presages a serious disturbance It is important to be able to establish such a deviation from normality at an early stage to devise adequate criteria for appraising the content of the symptom. This would not appear to be possible in the case of an individual age-conditioned symptom.

Parents often entertain an ideal picture of how a child should behave any deviation being interpreted as pathological The occasion of their

perplexity may be the expression possibly exaggerated of a normal developmental characteristic This is particularly probable in the case of age-conditioned symptoms Behaviour is evaluated in terms of what it signifies and whether it occurs at a later age A patently age-conditioned symptom such as temper tantrums or destructiveness takes on a new significance at 7-8 years as compared with the corresponding symptom at 3-4 years Only the daily occurrence of temper tantrums at 6 years and subsequently deviates sufficiently from the behaviour of the group to warrant closer attention

Behavioural changes are sometimes temporary due to anxiety associated with a particular situation such as an accident a spell in hospital a tragedy in the family or a brief passing conflict in the home After a few months or a year a quieter period ensues and the symptom is no longer manifest Symptoms of this kind may have a good prognosis notwithstanding the drama which may accompany their inception Stammering that appears in chronological relation to an accident is no less likely to disappear than stammering due to other reasons Thus no reliable predictions can be made concerning acute situation-conditioned symptoms either

As can be seen from fig.2-4 symptom persistence varie considerably Some symptoms (e g thumb sucking) represent a persistent pattern which changes very slowly By 4 years the habit is of long standing and leaves no room for surprising changes Nailbiting a symptom at the developmental stage in these years persists in a high percentage of cases and recurs with a strikingly high frequency Other symptoms such as tics and stammering which are presumably under further development later on are more capricious and unpredi tabl For the most part these symptoms are so new during the bservation period covered here that they come and go Day- and nightwetting should also be included in the group of symptoms which are non-predictable at 4 years This is all the more apparent when the lement of deficient maturity has been reduced. The number of children with encopresis is too small to permit an interpretation of the curve

SYMPTOM LOAD

INTRODUCTION

As pointed out above the individual symptom cannot carry more than a limited prognostic value Findings at 4 years are repeated for only some children at the age of 8 Deviant behaviour of the kinds considered here thus occurs frequently at a certain age without being a sign of persistent disturbances

But even if an isolated symptom at 4 years is frequently short-lived it seems worth investigating whether children who present several overt behavioural disturbances at that age do so later as well

Another hypothesis to be tested is whether symptom load co-varies with intelligence Observations along these lines have been reported namely that psychic morbidity is more common among former members of special school classes than it is among others (6) and that the number of problem children in a normal sample diminishes as I Q. rises (2)

Children s symptoms of maladjustment are sometimes blamed on mothers who go out to work and are regularly absent from the home Data have accordingly been analysed to test this with reference to the ten symptoms considered here

Method

With a view to testing the above a chart of symptoms comprising the ten forms a deviant behaviour mentioned previously was compiled for the children at 4 and 8 years of age Each of the 198 children has been accorded a score for each variable 0 denoting that the symptom has not occurred 1 that it has been observed but only occasionally and 2 that it has been present to a marked degree This simplified grading has been used for the sake of uniformity even if the observations of intensity would have permitted greater differentiation. Symptoms that occur daily" every week" "usually" and often have all been rated as 2

In this way each child has been loaded with a score between 0 and 20 at the ages of 4 and 8 A nine-fold table comprising all the individuals has been constructed to compare children with low medium and high symptom loads at the two ages Separate calculations have been made for each sex.

To test the co-variation with intelligence an analysis has been made of the symptom loads carried by children in the extreme groups: high

I (120 or more) and low I Q. (80 or less) using the standardised Terman-Merrill quotients at 5 and 8 years respectively

Information on the mothers gainful employment up to the children s 3rd birthday has been taken from form 0 (longitud) item 70 The mothers who had full or half-time employment at every investigation formed one group in the comparison the other group comprising the mothers who never had gainful employment during this period The remaining mothers in the sample had been registered as working on some occasion or else the information was incomplete; these two categories were consequently excluded from the calculations

Results

The mean symptom scores were as follows:

Girls at 4 years	6 ± 2 2
at 8 years	5 9 ± 2 3
Boys at 4 years	5 9 ± 2 2
at 8 years	5 1 ± 2 2

In comparisons between 4 and 8 years X^2 values were as follows:

Girls	21 170	p = 001 (4 df)
Boys	23 101	p = 001 (4 df)

There is thus a statistically significant probability of a child having a high score at 8 years if it has a high score at 4 The children who are relatively free of symptoms in the variables investigated here at 4 years have a better chance than those with a high sympton load of also belonging to the low scorers at 8 years The number of deviant symptoms is thus of predicative interest

The comparison between symptom loads (3 levels) and the extreme groups as regards intelligence at 5 and 8 years of age resulted in the following table:

Table 1. Intelligence and symptom scores

	Symptom scores At 4 years			At 8 years		
	0-4	5-6	7-13	0-3	4 5	6-13
I.Q. of 120 or more	7	6	7	9	8	2
I.Q. of 80 or less	4	2	11	3	6	8

The distribution in the sixfold table suggests particularly at 8 years of age that the least intelligent are those with the highest sympton load The differences in the present material are too small however to be statistically reliable (p = 20 resp 10 in X^2 values with Yates correction)

Data on the possibility of a connection between gainful employment by the mother when the child was very young and the symptom load of the child at 4 and 8 years are presented in Table 2

Table 2 Mothers gainful employment in relation to their children s sympton loads

	No of symptoms at 4 yrs		No of symptoms at 8 yrs	
	Average or more	Less than average	Average or more	Less than average
Part or full-time work at every investigation (1-3 yrs)	15	11	10	16
Never any gainful employment (1-3 yrs)	7/	38	54	58

Children whose mothers were orking full or part-time at every investigation between 1 and 3 years were not more loaded with symptoms at either 4 or 8 years of age than children whose mothers had never had gainful employment No co-variation could be demonstrated that might indicate a relationship

DISCUSSION

Many of the symptoms investigated here have been only temporary This possible runs counter to other reports in which the development of symptoms has been mapped in clinical cases To some extent at least the contradiction is more apparent than real The populations studied have varied in their composition. When changes in symptoms are studied on the basis of clinical cases after various methods have been used in the treatment of say stammering tics or sleep disturbances the symptom will usually have ex sted for a considerable time already and may even

have become fixed as an inaccessible neurotic symptom. The stability of the deviation will then differ from the stability in a sample of normal children where even the earliest manifestations of a deviation will be noted The instability in the development of the individual symptoms in the present sample is in keeping with the statement of Macfarlane et al (5) in their longitudinal study that the magnitude of interage correlations of problems suggests a nonpersistence over a long age span Similarly others have pointed out that early deviations are agebound phenomenon (4) or moderate predictors (3)

It is hardly surprising that a child with a large number of deviations at 4 years should be likely to have a large number at the age of 8 The variables in the analysis include some which have been shown to disappear slowly To some extent the symptoms of the other variables tested also persist between 4 and 8 years though only on a small scale But it is worth considering the predicative content in the amount (number) of deviant symptoms in the 4-year-old It is a sign that the lack of balance in the child s adjustment is more than temporary

Perhaps there is an element of stability in a propensity to react a flexible readiness to meet new situations (8 9) Each child makes individual attempts to find methods and develop a system for its adjustment to the internal and external environment There will be a risk of persistent symptoms insofar as this environmental pressure persists But since the family situation and childhood conditions change environmental pressure will vary and with it the child s reactions Clarizio (1) having reviewed various follow-up studies and retrospective studie published in recent years expresses his doubt as to a connection between early childhood maladjustment and later specific disability as follows: it would seem that change appears to characterize the course of behaviour deviations in children in as much as or more than, chronicity or stability" It is only when the results of longitudinal growth studies have been published from several quarters that the question can be given a more substantial answer

I am well aware that the behavioural variables chosen yield a limited picture of the child personality At this stage in the analysis of data my ambition has be

in the observations which the mothers have been able to report in a quantifiable manner concerning the children s behaviour Such information is an important but insufficient contribution to a full understanding the child s adjustment at these ages The symptoms may constitute a cry for help or a danger signal that flashes occasionally or more persistently They may be a reaction to a stress situation a defence that can also be interpreted as a healthy psychic reaction to an unsuitable internal or external strain They may represent a personal trait that is taken for a patholog cal sign. The concept of mental health and disease cannot be caught solely with the observable symptoms in the variables used or in other superficial variables.

Eventually a certain number of children will crystallize out from this normal child sample children whose previous data can be traced back in the wisdom of retrospect with a view to identifying the origins and causes of deviations in the development of their character and personality It will then be possible to evaluate the symptoms in a more balanced overall perspective This perspective as mentioned above will include personality tests and analyses of interaction with the environment the interpretation of which must be left to a future study

Summary and conclusions

Changes in the frequency of ten symptom variables have been followed in 198 children in the longitudinal Stockholm study by means of annual interviews between the ages of 4 and 8 years The following symptoms have been studied: night waking temper tantrums destructiveness finger sucking nailbiting tics stammering day wetting bedwetting and encopresis During these years notable changes occur in the symptom patterns of individual children. This is particularly the case with age-conditioned symptoms such as temper tantrums and destructiveness which become far less widespread by 8 years Symptoms diminish in other variables too with the exception of tics stammering and nail biting During the age period under consideration the latter three symptoms are of a more episodic and recurrent character than is e g finger sucking which is the most stable of all the symptoms

The symptom load in the above variables has been determined for every child at 4 years and at 8 years and a comparison has been made between the groups with the greatest and smallest loads It is not generally feasible to predict subsequent symptom developments on the strength of an isolated symptom in a 4 year-old If on the other hand the behavioural deviation is manifest in symptoms from several sectors of the 4-year-old s everyday life there is a far more patent risk of difficulties also occurring at 8 years

The accumulation of symptoms has been analysed in children belonging to extreme groups with respect to intelligence The distribution indicates a tendency for the least intelligent to have the greatest symptom load but the difference is no sufficiently great to rule out chance

The mothers who had regular employment when their child was 1-3 years old could not be shown to have a higher proportion of children with heavy symptom loads at children at 4 and 8 years of age than the mothers who never went out to work at that time

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CHAPTER XVIII

G E N E R A L S U M M A R Y

GENERAL SUMMARY

This study is part of a longitudinal prospective investigation of the growth and behavioural development of upwards of 200 children from Solna-Stockholm which has been in progress since 1955 The Stockholm study is part of a major international project sponsored by the Centre International de l'Enfance in Paris Similar investigations are being conducted in London Paris Brussels and Zürich and with regard to certain ages, in two African centres namely Kampala and Dakar Although the ultimate aim of the project is to elucidate the influence of different international cultural environments upon the physical and mental growth of children each research group has been confronted by the initial task of carrying out a preliminary analysis of the extremely comprehensive information systematically collected concerning the children in its own sample

Chapter I gives a list of papers comprising this thesis

Chapter II A longitudinal interdisciplinary study of this kind is a matter of teamwork. As a member of this team from the inception of the Swedish study the writer has participated in the planning of the investigation and participated in its current design. Interim results of the work of the study group have been presented in various quarters by different members of the team. A collective presentation of the Swedish project was published in Acta Paediatrica 1968 suppl 187 with studies of somatic mental and social changes during the first three years of the children s lives The essay in this supplement which I helped to prepare and design have been appended in reprint form to the present enlarged report covering the first eight years of the children s lives A summary of the content and results of these previously published essays is given in Chapters III and VIII This also includes summaries of two joint papers with contributions from all five European longitudinal CIE studies

Chapter IV General description of method, provides a tabulated account of the somatic mental and social information collected at different ages Most of the behavioural data on which the results presented here are based have been taken from structured interviews conducted by a psychologist Each of the three at some ages four inter-

view forms with mental data comprises 80 items Each item is provided with a variety of fixed alternative answers Certain variables contain up to ten different variations and gradings A consistent aim has been to secure actually observed behaviour if possible quantifiable and frequency-graded Interpretations and evaluations have been disregarded in as large extent as possible Expressions of temper and emotion have also been measured in terms of exemplified behaviour per day per week per month or more generally by expressions such as "usually" often sometimes seldom" or "never" The content of certain mental variables is naturally elusive

The development and intelligence tests used to elucidate relations to different behavioural variables have been Brunet-Lezine (up to and including 2 years) and Terman-Merrill (at 3 5 and 8 years) On the other hand the evaluation of the various personality tests is not yet complete Consequently these tests have not been used in the present study The child psychologist s assessment of the child in different fixed variables on a 5-point scale has been used to elucidate certain development characteristics The clinical findings of the pediatric specialist have also served as a background. Detailed social data have been collected annually and used for estimates of relations to mental data either as a condensed social score or as detailed particulars e g concerning housing conditions and the parents educational level

Chapter V deals with the los es to the sample occurring during the first eight years of observation. These comprise 12 cases (= 5 6 % of the original number) Six of these left the inve tigation because they moved far away one was killed in a road accident and the remaining five declined for various reasons to take any further part in the investigation Compared with other extensive longitudinal stu dies the loss is trikingly small

The loss is distributed between families with different social scores The resultant changes in the social and economic composition of the sample are negligible compared to the social improvements undergone by the families in 8 years The children born out of wedlock still constitute the same proportion of the sampl as before For has

the loss had any disproportionate effect on families whose mothers have a particular educational background.

Chapter VI provides a discussion on the advantages and disadvantages of prospective longitudinal investigations The cross-sectional investigation which is more commonly employed gives results more quickly costs less and is more easily made representative of the group of community it sets out to portray The loss of subjects in project which is inevitable and affects any continuous study of children over a period of several years is of no account in a cross-sectional investigation A longitudinal study must comprise a more limited number of subjects if the material is not to become too unwieldy No such limitation is necessary when the subjects are only to be investigated once A large and comprehensive material makes the statistical analysis more reliable and detailed.

But cross-sectional studies also entail certain obvious disadvantages The only possible way of elucidating the relations between previous events and subsequent processes in a child s life is to make a continuous study of the phenomenon to be followed. Parents memories are too selective and unreliable A prospective longitudinal approach is essential if the errors which have been found to exist in retrospective methods are to be avoided. The distance in time between observations must be relatively short and is one of the criteria of the reliability of a study Within reasonable limits unremitting observation is indispensable in evolving a model for the most reliable prediction possible concerning the development of a certain behavioural characteristic Given sufficient allround data, a continuous investigation from birth makes it possible to test theories concerning the causes of deviant behavioural development

A bodily measurement or a behavioural characteristic may be accomodated within the normal distribution limits in a cross-sectional investigation but the development of the individual child at the age in question may nonetheless deviate from the optimum development rate for which it is programmed. An assessment of growth and development should always be related to previous conditions and to a narrower time factor than usually is afforded by cross-sectional figures The results of

longitudinal studies of a representative number should therefore provide paediatricians or child psychologists with a more reliable frame of reference for prognostic development assessments

Chapter VII enumerates the methods used in the statistical analysis

The summary presented below comprises the analysis undertaken by the writer of limited portions of the collected material The extensive information provided by the data cards concerning the habits and behavioural characteristics of the children before they attained typical school age has been utilized to illustrate development during the pre-school years Particular interest has been devoted to the stability of the observed patterns of habits and the predictive value of the various symptoms A prominent place is given in the study to the interrelationships of different behavioural variables and their relation to environments of different kinds

Chapter IX on Non-nutritional sucking in ages from infancy up to 6 years of age deals with:

1. the frequency of finger sucking its stability and sex differences at different ages
2. its relation to feeding methods and the duration of mealtimes
3. its relation to different forms of behaviour in connection with feeding
4. the relation of prolonged finger sucking to emotional symptoms and social variables at the ages of 3-5 years
5. possible connections between finger sucking and malocclusion at 9-12 years and enunciation defects at 4-5 years
6. parental reactions to the sucking habit

Practically all children suck their fingers or comforters during the first six months of life There is a sharp fall in the frequency curve during the second half of the infancy period. After this period the number only declines slowly Finger sucking established at the end of the first year is strikingly stable Girls were significantly more prone to finger sucking than boys at every age level studied from 1 to 6 years.

There was no demonstrable significant covariation with feeding methods breast and bottle feeding made no difference The weaning age from all nutritive sucking the duration of the breast or bottle meal and the satisfaction it afforded were inversely related to the established habit of finger sucking to an extent which was more than coincidental The intensity of the sucking habit during the first sex months of life was of uncertain predictive value with regard to the fixation of the habit

The prolonged finger sucking group (= 5 years or more) was not particularly prone to stress symptoms or adjustment difficulties compared to the other children. The variables studied were: loss of appetite sleep speech fluency tics nailbiting the children s sensitivity liveliness and destructive tendencies On the other hand mothers employed solely in the home had more persistent thumb-suckers around them than mothers who had been gainfully employed during the first three years of the child s life (p = 01)

Thirteen per cent more children in the group with sucking habits had symptoms of malocclusion than in the group with minimal sucking or none at all The difference was not statistically probable but the trend was always the same even as regards special malocclusions The groups are too small to give any reliable statistical verdict Apart from this general tendency it was found that 6 of the children with prolonged thumb-sucking and 2 of the 9 most persistent dummy suckers were free from symptoms

Minor defects of enunciation were more common among thumb-suckers at 4-5 years than among other children (p = 01)

The mothers attitude to habitual finger sucking was generally very tolerant Intensive reactions to the habit were only noted in 5 % of the cases at the age of 5 years Mechanical countermeasures against thumb sucking were rare A considerable change has occurred in this respect during the past 20 years.

The results of the study do not provide any conclusive answers concerning the etiology of the occurrence and fixation of the habit either in terms of the theory of learning or other theories Some findings

but not all agree best with the theory of non-gratified instinctual needs The prolongation may be a learned behaviour

Chapter X. Nailbiting, deals with the age frequencies of nailbiting the persistence of the symptom and its co-variation with certain other behavioural variables The frequency of children biting their nails daily gradually increased during the pre-school years and had reached 5 % by the time they started school If nailbiting of less than daily intensity was also included the frequency of nailbiters at the same age was 40 % The sex difference at the ages of 5 and 6 years was significant at the 1 % and 5 % levels respectively with a frequency predominance by the girls

The symptom shows a clear tendency to recur even if it is more or less episodic during the observed years

No chronological connections could be established between the appearance of nailbiting and the cessation of thumb-sucking Nor was there any statistically significant relation between the rise in frequency at 7-8 years and the school start al hough the figures were significant at a level of almost 5 %. No covariation could be established with stammering tendencies tics tendencies temper tantrums or biting directed against other persons Of the variables tested, only exceptional defiance exhibited more than a random coincidence with nailbiting The covariation of defiance and nailbiting can corroborate the hypothesis that one of the initial causes of nailbiting at the pre-school stage is connected with inhibited aggression. Aggressive feelings which may not be expre sed freely are vented in thi way instead.

In contrast to biting directed against other persons habitual nail biting seldom prompted any strong parental reactions during the first 5 years Such efforts as were made to induce the hild to abandon the habit were not particularly successful Improvement and deteriorations were fairly evenly distributed.

The essay on Rhythmic movements in infancy and early childhood (Chapter XI) comprise a study of the tereotypes expressed in rocking (jactatio) and/or head banging This behaviour mostly began during

infancy when it was at least occasionally reported in more than half the children. None of the children in this series had begun later than 18 months Three per cent of the 200 children in the sample continued their rhythmic bedtime rocking without interruption at least until they reached school age

Head banging appeared as a habit associated with tiredness and as a symptom of emotional excitation Although despair and anger were the underlying and decisive emotion in the majority of cases there were also cases of children banging their heads to seek pleasure

The stereotypes of these kinds persisting at 3 years showed no statistical relation to habitual thumb sucking night waking or teeth grinding Nor did children sleeping in a room of their own exhibit more stereotypes than others

Even if head banging and rocking were prolonged habits and a disturbance to the child s surroundings almost all these cases have no more special symptom load than others When the bed rocking behaviour persists for an exceptional length of time it can be compared to a conditioned reflex for obtaining release and satisfaction.

Chapter III is entitled Expectation and re lity concerning toilet tra_ning A general account is given here of toilet training methods toge her with the point at which full control is achieved over bladder and bowels The chronological connection between the commencemen of training and functional control is studied together with the stability of the control thus achieved and the effect of coercion during toilet training The relation between the rhythm of the bowel functions during the first months of life and subsequent difficulties and conflicts duri_g training is tested

The latter part of the essay is devoted to a description of the occurrence development and covariation of primary and secondary forms of enuresis diurna and nocturna and encopresis A test is made of mean ability differences between groups with different forms of functional instability

The following results may be mentioned:

1 The median age for the first attempt at training was 8.4 months for the girls and 9 months for the boys

2. The median age for the commencement of continuous training was 10.9 months for the girls and 13 8 months for the boys The difference between these median ages is statistically probably significant

3 Day dryness occurred at a median age of 26 2 months for the girls and 27 9 months for the boys Night dryness was achieved by the girls at a median age of 27 6 months and by the boys at a median age of 28 5 months None of these differences was statistically significant

Bowel control was achieved by the girls at a median age of 20 months and by the boys at a median age of 25 7 months The sex difference is significant at a level of 1 %.

4. Children who began their training at an early age ($<$ 9 months) did not achieve steady day dryness sooner than other children. Disregarding lapses in training steady results were achieved on average 20 months after its commencement

5 Boys offered significantly greater resistance to training and their training had to be suspended more often. The peak was attained at 18 months when 25 % of the girls and 40 % of the boys who were undergoing training had had to suspend it

6 At the same time as the majority of mothers were sympathetic and flexible in their attitudes to the children s resistance no less than 23 % of the children in the sample had been regularly subjected to coercion at some point in their training between 1-3 years. Neither the mother s education gainful employment nor her previous experience of children accounted for any significant differences in the frequency with which coercion was used.

7 Functional control was not achieved more rapidly or with greater

certainty after the use of coercion. Children who were late and unstable were subjected to more coercion than those who became clean at an early stage

8 Children described during infancy as irregular in their bowel functions had a more problematic toilet training at the age of 2 years than those noted for regularity

9 Coercion during training was not matched by refusal to eat or a tendency to nervous twitches during the pre-school years Nor was it reflected by residual utterances of defiance after the conclusion of the training period. On the other hand there was covariation between coercive training and early speech impediments

10 The prediction of bedwetting day wetting and encopresis in the four-year-old child in terms of corresponding behaviour on the attainment of school age was uncertain.

11 No mean quotient differences according to Terman-Merrill could be established between day and night wetters respectively and other children. The few children with primary encopresis were of inferior ability to children with primary day wetting (significance 05)

Chapter XIII A prospective longitudinal view of early speech impediments in a normal child sample This study deals with defects of speech fluency (tendency to stammering) during the pre-school stage and enunciation defects as symptoms of delayed speech maturity or as isolated symptoms not connected with any previously known speech retardation.

1. Defects of speech fluency even in their more lenient and temporary forms occur more often in boys than in girls There is a definite statistically significant sex difference between 5-7 years Stammering" during the pre-school stage is often temporary and of a clearly episodic nature Many of the defects of speech fluency reported by mothers at 3-4 years are presumably due to the fact that

peech has not yet attained sufficient stability and fixed organi-ation so that it is relatively easily disrupted by environmental nfluences during the development phase

. chronological connection with an accident or some other defined rightening experience was established in 11 cases Apart from the-e presumable causal connections a significance test did not re-eal any greater tendency to stammering in other children who had uffered accidents or frights Speech defects arising in connection ith a dramatic experience known to the mother did not on average ast longer than those which begun independently of any such expe-ience

Speech reactions exhibited a significant covariation with conflicts luring toilet training simultaneously noted loss of appetite (in boys) nervous twitches (both sexes) masturbation (both sexes) bywetting shyness and temper tantrums (in girls) The first of these is interpreted causally the remainder as simultaneous reac-tions in different behavioural variables to emotional tension

No connection could be established with weaning difficulties finger sucking nailbiting bedwetting or encopresis nor with social sta-tus the mother s education or marital status (at the time of the child s birth) or the birth of a sibling

B Enunciation defects and speech maturity assessed by a psycho-logist on a structured 5-point scale at 3 and 5 years showed a sig-nificant (p = 01) sex difference at 3 years but not at 5 years The girls were superior the boys Half the hildren who spoke indistinct ly at 3 years were still speaking in an childish manner when they star-ted school with indi tinct enunciation and/or difficulties with par-ticular sounds lisping being the commonest defect

Speech retardation was less common among children whose parents were in the habit of reading to them. The test concerned reading habits noted at 2 years and speech retardation noted at 3 years (signifi cance 05)

Naturally enough, ignificant (p = 001) mean differences of ability

measured in normalized Terman-Merrill quotients at 3 years were established between speech-retarded children and others These differences however remained practically unaltered if the same children were compared again at 8 years Speech-retarded 3-year-old children, taken as a group are at a disadvantage compared with other children when they start school Although there were children with specific speech retardation whose measured test results improved considerably between 3 and 8 years the group exhibited a large element of general retardation

Chapter XIV Further studies of sleep behaviour (mainly 4-8 years) This study contains data concerning the number of hours children sleep on average their access to bedrooms of their own and the extent to which they sleep in their parents bedroom difficulties encountered in putting children to bed and night waking and sleep disturbances As regards the last-mentioned of these particular interest has been devoted to behaviour on waking together with the incidence of sleepwalking and nightmares

Average lengths of sleep together with standard deviations for different ages are graphic illustrated. The correlation between length of sleep in the same children at different ages between 4-8 years was far better than that between the ages under 3 years but the correlation coefficient did not exceed 50 for any of the ages compared

Only 10-15 % of the children had access to a bedroom of their own Generally they shared a room with a sibling or siblings but in some 25 % of the families the children were still sleeping with their parents at the age of 8 years All the children had sleeping places of their own yet a strikingly large proportion of them spent some part of the night in their parents beds By 8 years the percentage had fallen to 18 % There was a statistically probability that children in social group 3 spent part of the night in their parents beds more often than other children. The mother s gainful employment did not influence the frequency rate in either direction

Both night waking and bedtime resistance are characteristics often reported as persisting in the same children year after year but the

This persistence is elucidated in figures.

A distinction should be drawn between night waking and sleep disturbances if the latter are taken to mean that sleep is disrupted by an emotionally disturbed state At 4 and 5 years most of the children who wake during the night show no sign of fright or disturbance but rather a need of playful attention or of a visit to the toilet The majority of cases of night waking at these ages are assumed to be related more to physiological variations in the depth of sleep than to mental imbalance

This assumption must be qualified by the observation that certain environment variables above all the placing of the child in strange surroundings (hospital orphanage or with a non-relative) produces a relatively greater frequency of night waking than in children who have not had such an experience between 4-5 years (p = 02) A similar tendency exists at 4 years but is not significant (p = 10) Corresponding separation effects have previously in this study been established in children aged between 2-3 years

Persistent night waking and prolonged defects of speech fluency occurred simultaneously to a greater extent than could be ascribed to coincidence

The occurrence of sleepwalking and nightmares has been studied in children aged 6-8 years Both conditions are often a transitory phenomenon, Approximately every tenth child is reported as sleepwalking from time to time during the observation period, In those cases where the symptom appeared more frequently it showed a marked tendency to persist Sleepwalking occurred too often in the same children in conjunction with unpleasant dreams to be due to mere coincidence Since according to the EEG and EMG investigations reported in the literature sleepwalking never begins during dream leep this clearly statistically significant covariation is surprising Probably the same background factors that initiate sleepwalking have the effect on other occasions of imparting particularly frightening qualitie to dream 1

Chapter IV Temper tantrums and destructiveness A description is given of the occurrenc and   istence of symptoms in these two variab-

les from 4 to 8 years of age Both symptoms are markedly age-conditioned Their frequency declines steadily once the 4-year mark has been passed. A co-variation at the 5 % level is demonstrated between the variables at 4 years but not for the less frequent form of the symptoms observed at 8 years The boys are reported to be more destructive than the girls (p = 02) No sex difference has been found in the propensity for temper tantrums The content of the variables is discussed

Chapter XVI Tics in statu nascendi The questions dealt with in this essay concern the occurrence of tic-like symptoms up to the age of 8 years and the persistence and development of the symptom. A test is also made of the hypothesis of the relation between the early occurrence (at 3-5 years) of *affect-motoric unrest exceptional liveliness and* temper tantrum on the one hand and on the other the occurrence of tic-like twitches between the ages of 6-8 years

The prospective longitudinal investigation procedure is particularly well-suited for such a study Even milder forms can be included in the picture At an early age the commonest form is the incipient tic symptom which has not yet rigidified into a persistent and well-defined symptom.

Since tics are regarded as a symptom of emotional tension they have also been tested for covariation with other deviational and reactive forms of behaviour such as sleepwalking stammering and nailbiting Masturbation has also been related to tic symptoms

One s abiding impression on examining the longitudinal symptom chart of the various tic children is that in most of them the symptom occurs during definite periods sometimes with one or more years between them There were isolated cases where tics could be established as permanent from the age of 2 years but even in these children the frequency intensity was said to vary during the intervals between the annual interviews Symptom frequency in the group rose considerably throughout the observation period Tic-like symptoms were commoner in the boys than in the girls (p = 05)

The group of children noted at 3-5 years for general and exceptional

restlessness exhibited tic like symptoms i e twitches localized to certain muscle groups one or more years later to a greater extent than the group of more quiet children (p = 05) Alternatively one can say that the general "muscular language of the younger child indicates a greater risk of developing into an involuntary gesticulatory language in the older child.

At the same time it was noted that temper tantrum were not frequency-correlated with simultaneous or subsequent tic symptoms This observation suggests the hypotheses that both temper tantrums and tics provide a vicarious outlet for a rise in emotional tension

The covariation of the tic symptom with stammering and with sleep-walking at the ages of 6-8 years was significant at a level of at least 2 % Masturbation (in girls) also accompanied tics to a greater extent than can be due to coincidence This could not be established for the boys

There were no demonstrable relations to the nailbiting symptom which is probably of a different etiological nature Nailbiting is presumably more closely related to defiance reactions than tics which contain a more dominant element of anxiety and fear

Chapter XVII Symptom changes and symptom load A graphic presentation is made of the changes between 4 and 8 years of age in the occurrence persistence and recurrence of the following ten variables in the "pure longitudinal sample night waking bedwetting day wetting encopresis temper tantrums destructiveness disturbed speech flow tics finger sucking and nailbiting The changes are plotted on a logarithmic scale making it possible to compare the extent to which changes have occurred in different variables Some indication of the stability of symptoms can be derived from the values for the number of persistent and the number of recurrent symptoms The extreme cases in this respect are non-nutritive sucking and daily temper tantrums

In the light of the demonstrabl instability the prognosis is discussed for deviations from so called normal behaviour among these preschool children. Since the symptoms are noted when relatively fresh, the change in the population studied also reflect temporary deviations

that are conditioned by age and situations Such cases are hardly likely to be caught in follow-up studies of clinical materials on which experience of the prognosis has often been based in the past One should therefore be cautious when evaluating the results of cross-sectional population studies

The individual symptoms followed up longitudinally have thus been found to have only a limited predictive power On the other hand an accumulation of deviations in the individual child at 4 years of age is followed to a large extent by a corresponding symptom load in the variables tested at the age of 8 The probability of this occurring is not attributable to chance (p = 001) The observation is discussed with reference to other studies

A comparison of symptom loads between extreme groups of children as regards intelligence indicates that the less intelligent had greater symptom loads at both 4 and 8 years of age but the difference was not sufficient ~eat to rule out coincidence (p = 10)

The symptom load at 4 and 8 years in children whose mothers had had regular employment when the children were small (1-3 years old) proved to be the same as the symptom load in children whose mothers had never had gainful employment at that time

APPENDIX

The questionnaire forms that were used at ages up to 3 years have been reproduced on pages 142 – 170 in Child Development An international method of Study Modern Problems in Pediatrics Edited by Frank Falkner S Karger New York. The item numbers and digits correspond to the references given in the present work except that part I in the above publication corresponds to the form designated no V in the Swedish study part II to form VI and part III to form VII

Excerpts from the questionnaire form for ages 4-5 years are given below with the numbers used for reference in the main text; in the case of items and digits that are exactly the same reference is made to the above publication

The arrangement and numbering of the items was changed at 6 years. The relevant excerpts from the questionnaire forms at 6-8 years are therefore reproduced below

Form V at 4 - 5 years

		Dig
V: item 14-30	= V: item 14-30 at 0-3 years	
V: 67	Does he ever stutter or stammer?	
	nil	0
	occasionally	8
	often	9
V: 68	Is there any difficulty with his talking?	
	nil	0
	often	1
	talks too much	2
	bad accent	3
	swearing	4
	lisping/lalling	5
	babyish	6
	stuttering	7
	difficult to understand	8
	backward	9

Form VI at 4 - 5 years

VI: item 11-21	= VI: item 11-21 vid 0-3 years	
VI: " 24-29	= VI: " 24-29 "	
VI: 38-40	= VI: 38-40	
VI: 42-46	= VI: 42-46	
VI: 47-50	= VI: 47-50	
VI: 52-59	= VI: 52-59	
VI: " 61-72	= VI: " 61-72 " "	
VI: 75-76	= VI: 75-76	
VI: 77	Does he ever sleep in your bed?	
	never	0
	less	1
	odd periods	2
	1 m or more: 1-2/w formerly	3
	1-2/w still	4
	sev/w formerly	5
	sev/w still	6
	nightly formerly	7
	nightly still	8
	always	9

Form VII at 4 - 5 years

VII: item 57: 7 8 9	= VII: item 55 at 3 years	
VII: 54	Does he often get into a tantrum? (Really marked temper)	
	never	0
	mild temper only	3
	less	4
	1 or 2/week	5
	sev /week	6
	1 or 2 daily	7
	several daily	8
	many/day	9

		Dig
VII: item 55	How shown?	
	none of these	0
	lies on floor	2
	stamps	3
	slams doors	4
	hits inanimate objects	5
	hits people	6
	shouts	7
	throws things	8
	abuses M or F	9
VII: item 56	How shown? (continue)	
	screams	11
	bites	1
	rigid	2
	thrashing limbs	3
	pinches	4
	scratches	5
	hits	6
	hurts self	7
	blue in face	8
	other	9
VII: item 57	Parents reaction?	
	smack	11
	(never angry)	0
	other punishment (specify)	1
	reproach	2
	ignore	3
	laugh	4
	divert attention	5
	give own way	6
	comfort	7
	isolate	8
	other	9

VII: item 58-59 at 4-5 years = VII: item 58-59 at 3 years

VII: 75	Is he lively or quiet?	
	unquiet	4
	lively	5
	rather lively	6
	medium	7
	rather quiet	8
	quiet	9

Fo n V at 6 - 8 years

	never	rarely	some-times	often (or for 2 months)	always
Feeding					

Sleeping					
Item 16 Has he made a big fuss about having to go to bed?	0	1	2	3	4
Item 21 Has he ever wakened in t night? (after you have gone to bed)?	0	1	2	3	4
Item 22 Has he ever had bad dreams?	0	1	2	3	4
Item 23 Has he ever walked in his sleep?	0	1	2	3	4

Toilet	never	rarely	some-times	several times a week for 2 months or more	always
Item 24 In the daytime has he soiled? (lost bowel control)?	0	1	2	3	4
Item 25. At night time has he soiled? (lost bowel control)?	0	1	2	3	4
Item 26 In the daytime has he wet himself (lost bladder control)?	0	1	2	3	4
Item 27 At night time has he wet himself (lost bladder control)?	0	1	2	3	4

Habit	never	rarely	some-times	1 or 2 a day (for 2 months or more	several times a day
Item 32. Has he sucked his thumb or fingers	0	1	2	3	4
Item 33 Has he done any nail-biting?	0	1	2	3	4
Item 36 Have you seen him holding or playing with his privates?	0	1	2	3	4
Item 37 Have you seen any twitching blinking tics or other "nervous movements	0	1	2	3	4

Fears

Speech	never	rarely	some-times	often (or for 2 months or more)	always
Item 46 Has he stuttered or stammered?	0	1	2	3	4
Item 47 Has he often had difficulty in getting words out?	0	1	2	3	4

Are there some sounds which he cannot say properly?

What?

General behaviour

- - - -

Item 50 Is he often defiant when corrected	0	1	2	3	4
Item 57 Does he break things on purpose?	0	1	2	3	4
Item 60 Is he sometimes timid with other children?	0	1	2	3	4

	never	less	1 or 2 a week	several times a week	daily or mor
Item 62 How often does he get into a real tantrum? (uncontrollable rage - not ordinary little tempers)	0	1	2	3	4

- - - -

Item 66 Sleeping time?

	Dig
no investigation	0
less	1
7 hours	2
8	3
9	4
10	5
11	6
12	7
13	8
more than 13 hours	9

		Dig
Item 67	Bedtime?	
	no investigation	0
	at 6 p m or earlier	1
	7	2
	7 30 p m.	3
	8	4
	8 30	5
	9	6
	9 30	7
	10	8
	11 or later	9
Item 68	Awakening time?	
	no investigation	0
	at 4 p m. or earlier	1
	5	2
	5 30 p m.	3
	6	4
	6 30	5
	7	6
	7 30	7
	8	8
	9 or later	9
Item 69	Does the child sleep in parent s bed?	
	no investigation	0
	in F's bed never	1
	seldom	2
	sometimes	3
	often	4
	in M's bed never	5
	seldom	6
	sometimes	7
	often	8
	always	9

Social form (O) is the same as published in the abovementioned Modern problems in pediatrics A special condensed form (long comprising social data from the first 3 yrs has been made Thi is given below

C born in year	item	11	
month		12	
Mother s age at C s birth yrs		13	14
Father s		15	16
Time relation marriage/C s birth		17	
Completeness of family during C s first 3 yrs		18	
Residency when C 3 yrs		19	
M's occupational status during C s first 3 yrs		20	
C s birth order among living born siblings		21	
C s order among siblings at home at birth		22	

When C is		1 yr	2 yrs	3 yrs
Number of children at home	item	23	42	61
Number and sex of older siblings at home or fosterhome		24	43	62
Number and sex of younger siblings at home or fosterhome		25	44	63
Swedish social classification		26	45	64
Graffar system:				
Occupation British (M s highest)		27	46	65
Occupation modified ( )		28	47	66
Education		29	48	67
Sources of revenue		30	49	68
Income grouping		31	50	69
Dwelling		32	51	70
Total scoring original		33-34	52-53	71-72
Total classification original		35	54	73
Total scoring modified		36-37	55-56	74-75
Global classification modified		38	57	76
Income magnitude in 100 krs		39-41	58-60	77-79
M s education when C 3 yrs				80

Some used code for Social form (long.), sum for the first 3 years

C born in month

Dec	12	12
Nov	11	
Oct	0	
Jan	1	
Febr	2	
Sept	9	

Time relation marriage/C:s birth

unmarried	0	17
within 1-8 months after marriage	1	
" 9-23	2	
3 rd year of marriage	3	
4 th	4	
5 th	5	
6 th	6	

Completeness of family during C:s first 3 years

	in fosterhome at 3 yrs	12	18
at C:s birth:	M married F later divorced and later married another man	11	
	M married F not divorced	1	
	M later separated	2	
	M later divorced	3	
	M unmarried living with F later married F	4	
	M unmarried living with F continuously	5	
	M unmarried living with F later separated	6	
	M unmarried living single continuously	7	
	M unmarried living later on with another man	8	
	M unmarried married later on another man	9	

Residency, when C 3 yrs

living in Solna	1	19
in Stockholm and inner suburban area (not Solna)	2	
in outer suburban area of Stockholm	3	
outside of Greater Stockholm in town	4	
in rural	5	

M:s occupational status during C:s first 3 yrs

information lacking for any of the three investigations	12	20
full-time occupation at each investigation	1	
full-time or part-time occ at each investigation	2	
never any occupational work	3	
rest (= did occupational work on some occasion)	4	

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BY JÖRGEN SILWER

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM SWE

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SUPPLEMENTUM 238

FROM THE COAGULATION LABORATORY (HEAD: PROFESSOR INGA MARIE NILSSON, M.D.) UNIVERSITY OF LUND, ALLMÄNNA SJUKHUSET, MALMÖ AND THE PÆDIATRIC DEPARTMENT (FORMER HEAD: DOCENT STEN AXTRUP, M.D.) CENTRALLASARETTET, KRISTIANSTAD, SWEDEN

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HISTORICAL

von Willebrand's publications

It was in 1926 that von Willebrand published his first description of a familial haemorrhagic diathesis, occurring in both sexes and characterised by a prolonged bleeding time despite normal platelet count. He called the disease hereditary pseudohaemophilia.

His report included a survey of 19 previously published cases with a similar clinical picture. The earliest case that he could trace was one presented by Kehrer as early as 1876.

von Willebrand's *first case was seen in a girl*, Hjördis S. When first examined she was 5 years old. She belonged to a *sibship of 10* children, some of whom had had more or less pronounced bleeding symptoms. Three of the sisters had died at *2–4* years of age from bleeding. Both parents had, when young, had troublesome nose-bleedings.

On further investigation von Willebrand discovered several relatives of Hjördis S. with symptoms of the same haemorrhagic diathesis, and as early as 1926 he published data about 23 bleeders. The family now the well known Åland family has since been studied more extensively (Eriksson et al. 1961) and is still the one with by far the largest number of members with known von Willebrand's disease.

In his publication von Willebrand gave very good description of the clinical picture of the disease. The dominating symptoms consist of nose-bleeding, gingival bleeding, uterine bleeding and cutaneous bleeding in the form of ecchymoses and haematomas. Gastrointestinal haemorrhage is relatively uncommon, but when it occurs, it is often serious. von Willebrand also pointed out that, in contrast with what is seen in haemophilia, joint bleeding in the Åland family was rare.

von Willebrand also carried out laboratory studies, which must be regarded as extensive for that time.

The bleeding time, as determined by the method of Duke, was prolonged to more than two hours in the severest cases, including the first one in Hjördis S. In several of the other affected relatives the bleeding time was normal.

The coagulation time was invariably normal. Clot retraction was studied only in Hjördis S. and was found to be normal. The Rumpel-Leede phenomenon showed capillary resistance to be impaired in patients affected.

In investigation of the heredity of the bleeding tendency von Willebrand consulted a geneticist, Federley in *Helsingfors. They arrived at the conclusion that the* condition was transmitted by a dominant sex-linked gene, linked to the X-chromosome. *This conclusion* was supported by the fact that von Willebrand had found bleeding symptoms more often in females and that all of the severe cases were seen in females, especially those with a fatal issue. These patients with severe haemorrhagic diathesis were thought to be homozygous in respect of the bleeding tendency.

von Willebrand compared the condition with other more well-known bleeding diseases, especially classical haemophilia, which, however occurs only in males. It differs furthermore from the bleeding disease in Åland by a prolonged coagulation time and a normal capillary resistance.

Finally von Willebrand (1926) discussed the pathogenesis of the condition and found that the bleedings could best be explained by the joint effect of a functional disorder of the platelets and a systemic lesion of the vessel walls.

The first publication on the bleeding disease, which now carries his name, was written in Swedish, *In 1931* he published a second article of the subject, which was written in German and was thereby accessible to a larger number of readers.

In order to form a conception of the possibly disturbed vascular function, von Willebrand (1931) had Hjördis S. examined with capillary microscopy. The investigation showed considerable fluctuation in the blood flow through the capillaries, which were tortuous with variation in the caliber and contraction of the loops, von Willebrand, however pointed out that tortuous capillaries occur also in other diseases, e.g. such vascular affections as arteriosclerosis and nephritis.

In that article he also published a small section on therapy. He felt that blood transfusions were useful not only for replacing blood loss, but also for controlling bleeding.

In the beginning of the 1930s von Willebrand contacted the German researcher, R. Jürgens, who had together with Morawitz *(1930)* described a so-called capillary thrombometer for measuring the "thrombo-

tion time. With this apparatus blood is pressed to and fro through a glass capillary tube. This results in the formation of a plug, which normally occludes the capillary after about 4 minutes. The so-called thrombosis time was, according to Morawitz and Jürgens, well correlated with the bleeding time but not with the coagulation time. On microscopic examination the plug was found to consist mainly of platelets.

von Willebrand and Jürgens together studied members of the Åland family with the use of the capillary thrombometer (von Willebrand & Jürgens 1933 a). The thrombosis time for Hjördis S. and some of her relatives was found to be extremely prolonged, up to 30–40 minutes, while in the other bleeders examined the time was prolonged by only a few minutes or was even normal.

As to the heredity of the disease, von Willebrand 1933 revised his previous opinion and now thought it to be due to an autosomal dominant gene. He thus no longer believed in a sex-linked dominant heredity with the gene linked to the X-chromosome, partly because he had seen cases where the bleeding tendency had evidently been inherited from father to son, while the mother had apparently not been affected.

von Willebrand and Jürgens felt that their findings with the capillary thrombometer suggested that the pathogenesis of the disease can be assigned largely to a functional disorder of the platelets with reduced agglutinability and consequent deficient formation of platelet plugs. They therefore called the disease constitutional thrombopathy, a name which was later widely used, particularly in the German literature.

The authors distinguished constitutional thrombopathy from the disease, which had been described by Glanzmann (1918). In the latter disease clot retraction was regularly abnormal and the platelets showed considerable morphological changes not seen in the disease in the Åland bleeders.

Further studies on von Willebrand's disease and similar conditions

From the middle of the 1930s until the middle of the 1950s several cases of hereditary haemorrhagic diseases with prolonged bleeding time and normal platelet count were reported from Europe and U.S.A.

A large compilation of such cases has been published under the title of "Pseudohemophilia" by Buchanan and Leavell (1956) (199 cases including 13 personal cases). Clot retraction is said to have been normal in the vast majority of these cases. Most of them were probably examples of von Willebrand's disease, this being the commonest of the hereditary haemorrhagic diathesis with prolonged bleeding time now seen at most large coagulation laboratories.

In the discussion of the pathogenesis, especially during the 1940s and 1950s, much space was given to the observations made by Macfarlane and described by him in his article, Critical Review: The mechanism of haemostasis (Macfarlane 1941). Under the name of athrombocytopenic purpura he reported cases of a hereditary bleeding disease with prolonged bleeding time and normal platelet count. He compared this form of bleeding disease with those described by von Willebrand and Glanzmann. He himself examined 5 such cases with capillary microscopy and found that the capillaries were both anatomically and functionally abnormal: they appeared to be tortuous and often bizarre, and they did not contract in a normal way after microtrauma. Macfarlane therefore considered the disease to be of vascular origin and rejected von Willebrand's and Jürgens theory supposing platelet deficiency as the main cause of the bleeding symptoms.

Findings like those described by Macfarlane have since been made in similar morbid conditions (O'Brien 1951, Alexander & Goldstein 1953, Schulman et al 1955, Singer & Ramot 1956 and others). Some authors, however, did not find the capillaries in so-called pseudohemophilia to be abnormal (Estren, Medal & Dameshek 1946, Jamra et al 1952, Braunsteiner 1955, Verstraete & Vandenbroucke 1955, R. Jürgens 1956, Sharp & Ellis 1960).

In 1947 Quick described a method for determining prothrombin in serum as a measure of prothrombin consumption. With this method he was able to demonstrate slight disturbances in the earlier phase of coagulation, disturbances which are not reflected in prolonged coagulation time.

In 1951 Jürgens and Forsius (R. Jürgens & Forsius 1951) found a reduced prothrombin consumption in 6 patients of the Åland family, while in other, less severe cases it was normal.

They felt that the low prothrombin consumption was probably due to disturbed function by a platelet enzyme involved in the formation or activation of plasma thrombokinase.

A platelet factor with this effect has since been known under the name of platelet factor 3.

Detection of low AHF and deficiency of an antibleeding factor in von Willebrand's disease

In the beginning of the 1950s improved methods were devised for determination of the antihaemophilic factor which corrects blood coagulation in haemophilia A and whose existence had been shown by *Patek & Stetson (1936)* and *Patek & Taylor (1937)* and others.

The most widely known method is the one described by Biggs & Douglas (1953) as the thromboplastin generation test. This test made it possible readily to distinguish haemophilia A from haemophilia B and to estimate the content of the antihaemophilic factor (AHF).

The same year *i.e.* in 1953, three reports appeared of cases with decreased AHF in bleeders with a prolonged bleeding time despite normal platelet count, *i* with a clinical picture often described as characteristic of pseudohaemophilia. The reports were given by Alexander and Goldstein (1953), Larrieu and Soulier (1953) and *Quick and Hussey (1953)*. *Similar findings in this* type of disease were later described by *e.g.* van Creveld et al. (1955), Schulman et al. (1955) and Singer and Ramot (1956).

In 1956 I.M. Nilsson et al. (1956) described a case (Birgitta) and its treatment with AHF and Fraction I–O. The condition was entitled female haemophilia because the *girl had been found to have a considerably* reduced content of AHF – down to 1–5 % of the normal. But the condition differed from classical haemophilia in two respects: it was seen in a female, and the bleeding time was noticeably prolonged. The patient had previously had several episodes of bleeding such as nose bleeding, gingival bleeding and bleeding from the sockets after tooth extractions. From menarche the disease had assumed a serious character with life-threatening menorrhagia. Blood transfusions produced only temporary improvement of the blood values and finally caused severe symptoms of sensibilisation.

The authors therefore decided to try the effect of human Fraction I–O from Cohn's Fraction I (Blombäck & Blombäck 1956), a preparation in which the antihaemophilic globulin *activity of the original plasma was* almost completely preserved.

A test dose of *Fraction I–O corresponding* to the AHF-content of 2,500 ml blood promptly controlled the bleedings from the gingiva, from a pin prick in the ear and from the uterus. The coagulation time and the bleeding time became normal and the AHF content of the plasma increased to 55%. After 48 hours half of the injected AHF-activity was still demonstrable.

Four days later the patient received another dose of Fraction I–O and the next morning hysterectomy was performed without any increased bleeding tendency.

During the following years Nilsson and co-workers found several similar cases. By 1959 they had examined in all 26 patients belonging to 20 different families. The females were affected to the same extent as men (Nilsson, Blombäck & Blombäck 1959).

Treatment with Fraction I–O was tried on several of these patients in association with episodes of acute bleeding or at operation: such treatment invariably had a favourable effect with an increase of the AHF content and shortening of the bleeding time, often to normal values. Also the clinical results were very satisfactory.

Fraction I–O contains not only AHF but also fibrinogen in high concentration. Administration of purified fibrinogen produced no effect on the AHF level or bleeding time of the patients. Purified AHF Fraction I–1 A (Blombäck and Blombäck) had no effect on the bleeding time either. On the other hand, AHF-free Fraction I O prepared from plasma of patients with severe haemophilia A shortened the bleeding time.

The authors (Nilsson, Blombäck & von Francken 1957) concluded: "Taken together these observations could indicate that the prolonged bleeding time in this syndrome is caused by deficiency of a vascular *factor*" which is present *in* Fraction I–O and not identical with AHF or fibrinogen.

As for the increase in AHF-activity it was found to exceed that expected from the amount of AHF given with Fraction I–O (Nilsson, Blombäck & Blombäck 1959). The highest activity level was not noted immediately after the infusion, but after several hours. It then gradually fell and reached normal level after several days. It was also found that Fraction I–O from haemophilia A-patients with an AHF-content of only 1–2% raised the AHF-level in one patient from 6 to 19 % of normal value. It was therefore concluded that the above-mentioned factor not only affected the bleeding time, but also *stimulated the production of AHF*.

The effect of treatment on the bleeding time was of shorter duration than that on the AHF-production and a markedly prolonged bleeding time had often returned to original values within less than a day (Nilsson, Blombäck & Blombäck 1959).

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Studies of the platelets of the patients revealed no platelet defect. Even platelet factor 3 was found to be normal (Nilsson, Blombäck & von Francken 1957).

Further infusions of washed platelets from normal persons were given but without any effect on the bleeding time

On careful examination of the families the authors found that the patients with a tendency to bleeding always had one parent with reduced AHF-content while the other parent and his or her family had normal values. It was found that the AHF-deficiency was inherited as an autosomal dominant gene (Nilsson, Blombäck & von Francken 1957)

The bleeders traced in Sweden resembled those belonging to the large families of bleeders in Åland in respect of heredity symptoms and prolonged bleeding time. But in the Swedish cases, in contrast with those from Åland platelet function was not impaired.

In 1957 Nilsson and co-workers therefore went to Åland and studied the patients belonging to the Åland family including some who had been examined 25 – 30 years previously by von Willebrand himself (Nilsson et al 1957). They found the AHF values to be decreased, but the platelet factor 3 to be normal. One of the patients from Åland was given Fraction I-O which controlled the coagulation defect and the bleeding time. These investigations had thus for the first time shown that the disease, which in several quarters had been described as being characterised by a reduced AHF-content and prolonged bleeding time, was identical with von Willebrand disease

The same year Jürgens et al also showed the AHF content often to be reduced in the Åland bleeders (R. Jürgens et al 1957). The deficiency of this factor has since been regarded as a characteristic if not an obligatory feature of the disease

Fraction I-O was afterwards used widely by Nilsson and Blombäck in the treatment and prophylaxis of severe forms of von Willebrand's disease. In mild cases and in less acute situations it proved sufficient to use fresh plasma or freshly frozen plasma (Nilsson 1965)

The results obtained on administration of different sorts of plasma and plasma fractions in von Willebrand's disease have since been widely confirmed by several researchers (Cornu et al 1961 and 1963, van Creveld et al. 1963, Borchgrevink et al. 1963, Barrow and Graham 1964, Ikkala, Myllylä & Nevanlinna 1964, H. Perkins 1967 and others)

Among others, Cornu and co-workers have shown that haemophilia A-plasma, like normal plasma, contains the factor that stimulates AHF-production in von Willebrand's disease. But no such effect is produced by transfusion of plasma from a patient with von Willebrand' disease to one with haemophilia A

These observations have given rise to much speculation on AHF-synthesis in the two diseases, seen largely from a genetic point of view

Graham and Barrow published investigations (Graham 1959, Graham, Barrow and Roberts 1965) based partly on the Swedish von Willebrand-series. They pointed out that in many cases prolonged bleeding time and reduced AHF-content are not seen together and that the symptoms may perhaps be inherited by different genes

Investigations of von Willebrand's disease since the latter half of the 1950s

During the 1950s and 1960s von Willebrand's disease received increasing attention. Cases were reported from most countries in Europe as well as from different parts of the world, such as Chile (Larrain and Bancalari 1965), South Africa (Gomperts et al. 1969), India (Kasliwal et al 1966), Japan (Yamada et al. 1965) and Australia (Castaldi et al. 1967)

The frequency of the disease is now approaching or exceeding that of haemophilia (Horowitz & O'Leary 1965, Quick 1967a, J. Jürgens 1969)

The increase in the frequency of recognised cases is due to some extent to the use of Ivy's method for determining the bleeding time (Nilsson, Magnusson & Borchgrevink 1963, Silwer & Nilsson 1964, Ascari, Barbieri & Gobbi 1964, Cornu 1965, Abildgaard et al. 1968 and others). This method especially Borchgrevink and Waaler's (1958) modification of it, has proved sensitive and valuable and has revealed an increased bleeding tendency in many mild cases with a normal bleeding time with the Duke technique

Cases of a hereditary bleeding disease with prolonged bleeding time, as in von Willebrand's disease, have been reported, but with normal values for AHF and a low content of haemophilia B-factor (Achenbach & Klesper 1957, Combrisson-Le Bolloch, Debray & Benhamou 1957, Soulier & Larrieu 1957, Gugler 1960, Blackburn et al. 1962, Mey & Panzram 1962, Winckelmann & Walther 1964, Wake & McClure 1965, Schweiberer, Wendlberger & Licht 1966, Özsoylu & Corbacioglu 1967 b)

In the 1960s attention was directed to, above all, platelet dysfunction

Especially German investigators have given attention to the supposed deficiency of platelet factor 3. The idea of a true defiency has been more or less re-

placed by the assumption of an inhibited release of the factor in question (Johnson, Monto & Caldwell 1958, Landbeck & Uathavikul 1959 Eriksson et al. 1961 Winckelmann & Walther 1964 and others)

Among others, Eriksson and co-workers have found electron microscopic changes in the granules of platelets, which they believe to constitute the morphological basis of the reduced platelet factor 3 activity

In the Anglo-American, Scandinavian and French literature much interest has been devoted to a reported decreased platelet adhesiveness and platelet aggregation in von Willebrand's disease.

The methods for determining platelet adhesion to glass have been improved by Hellem, who pumped citrated blood through plastic tubes filled with glass beads (Hellem 1960). Hellem examined a few patients with von Willebrand's disease, but found no certain decrease in platelet adhesiveness. Later however Salzman (1963) modified the method by inserting the tube with the glass beads between the needle for venous puncture and a vacuum tube containing EDTA. In this method, directly after puncture the platelets pass over the beads before they come into contact with the anticoagulant. With this set-up the flow rate is increased. Salzman regularly found the platelet adhesiveness to be decreased in patients with von Willebrand's disease. Salzman's findings have since been confirmed by various workers (Strauss & Bloom 1965 Bennet & Dormandy 1966, Lemoyne & Larrieu 1967 H Perkins 1967 and Abildgaard et al. 1968 and others)

Borchgrevink (1960) in Norway who used an "in vivo-method" for measuring platelet adhesiveness found results compatible with Salzman's ones.

The observations made have since been related to the anti-bleeding factor in normal plasma, demonstrated by Nilsson et al. It has been thought that it is via the platelets that this factor exerts its action by influencing their adhesiveness and aggregation (Ödegaard, Skålberg and Hellem 1964 b, Owren 1965).

Especially French researchers (Larrieu et al. 1968 Meyer & Larrieu 1970) have found that administration of normal plasma and plasma fractions to patients with von Willebrand's disease causes a correction of the decreased platelet adhesiveness parallel with the suppression of the bleeding tendency

In 1960 Hellem described a factor R, which influences adhesiveness of platelets in normal plasma. This factor has since been identified by Gaarder et al. (1961) as ADP

Norwegian and French researchers have studied the effect of ADP also on platelet aggregation and reported an abnormal reaction to ADP in low concentrations in patients with von Willebrand's disease (Ödegaard, Skålberg & Hellem 1964 a, Vainer & Caen 1964). Some of these experiments were repeated on a large series of patients with von Willebrand's disease by Cronberg, Nilsson and Silwer (1966), who however were unable to find any difference in the reaction of these patients and normals.

Therapeutically many investigators have used Pool's cryoprecipitate, which is said to have essentially the same effect as Fraction I–O (Bennet & Dormandy 1966, Castaldi et al. 1967 Dana 1967 H. Perkins 1967 Abildgaard et al. 1968, Walker & Dormandy 1968, Rizza & Biggs 1969 Kemp, Nolan & Carpenter 1970).

Moreover various hormone preparations have been tried, e.g cortisone and related steroids (B Jacobsson 1953, 1957 Schulman et al. 1956, Bernard et al. 1957 Cornu et al. 1961 Lemoyne & Larrieu 1967 Ponka, Monto & Welborn 1967 and others) Further in the treatment of bleeding from the female reproductive organs preparations of different types of sex hormones have been used, even p-pills (Achenbach 1960, Barrow & Graham 1964, Bonechi & Pasero 1964 Akman et al. 1965 Özsoylu & Corbacioglu 1967 b, van Crevald & Sheffekens 1969 and others)

Thus, especially in the last decades, von Willebrand's disease has received increasing space in the literature. The combination of prolonged bleeding time and deficiency of one of the widely known clotting factors, AHF is difficult to explain The so-called von Willebrand-factor which is found in Fraction I O can be postulated from its known effects. The chemical nature and mechanism and mode of action of this substance is, however not properly understood. Its possible significance in such diseases as thrombosis and arteriosclerosis has also been discussed (Owren 1965, Silwer Cronberg & Nilsson 1967). As for the significance of platelets in the pathogenesis of von Willebrand's disease, opinions still differ

Wide experience has accumulated through the years as to the clinical picture of the disease, its symptoms, risk of bleeding in various situations, diagnosis, possibilities of treatment and prognosis. Utilisation of this experience should prove of great help to physicians in the recognition and treatment of cases encountered in their practical activity

MATERIAL AND METHODS

MATERIAL

The material consisted of all patients with a firm or highly probable diagnosis of von Willebrand's disease and seen at the Coagulation laboratories in Malmö, Stockholm or Gothenburg in the years 1956–1967.

Inquiries were made into all of the families of the patients included in the investigation. When possible, laboratory studies were made of the closest relatives of the probands, particularly their parents, siblings and children. The material presumably includes all known cases of von Willebrand's disease in Sweden up to the end of 1967. The diagnosis requires special laboratory facilities, at present available only in Malmö, Stockholm and Gothenburg.

The investigation included a careful inquiry into the probands' history regarding bleeding symptoms and the information obtained was, as a rule, supplemented by data from earlier hospital records in those cases in which the patient had sought medical advice or had been admitted to hospital because of their haemorrhagic symptoms.

In most cases, and particularly in probands, a complete investigation was made of the patient's bleeding [illegible] gulation status.

Examination of relatives of the probands was often limited to determinations of the bleeding time according to Duke and Ivy and of the AHF.

The probands were all examined several times and at least on one occasion during a period when they were not bleeding. Relatives were also often examined more than once, especially in doubtful cases.

METHODS

Interest was focused mainly on determinations of AHF

Bleeding time according to Duke and Ivy

Platelet adhesiveness according to Salzman

AHF-determinations

Blood sampling – Venipuncture was performed with sharp, wide needles with a polished bore (caliber 1.2–1.6). The first few millilitres were discarded, and the blood was allowed to flow directly through the needles into the tubes.

The blood was collected with the silicone technique. Citrated plasma (one part 3.8 % trisodium citrate solution x 2 H_2O + 9 parts blood) and serum were prepared by methods, described previously by Nilsson et al. (Nilsson, Blombäck & von Francken 1957, Nilsson, Blombäck, Thilén & von Francken 1959 and Paraskevas, Nilsson & Martinsson 1962). The blood was immediately centrifuged at 2,300 g for 25 minutes at room temperature. Plasma was withdrawn by means of siliconised pipettes and immediately frozen in plastic tubes at −20 – −60 C.

The plasma antihaemophilic factor (AHF or factor VIII) was assayed on platelet-rich haemophilia A plasma (AHF-content < 1 %) in a recalcification system, in which the ability of the citrated control plasma and of the test plasma to correct the prolonged recalcification time of citrated haemophilia A-plasma was compared. The haemophilia A-blood was drawn with the silicone technique and centrifuged without delay at about 700–1 000 g for 10 minutes. It was checked that haemophilic plasma contained at least 200,000 platelets per cu.mm. The plasma was then distributed in plastic tubes and stored at −20° – −60° C (it was usually used within 2 weeks). This method has been described and commented upon by Nilsson et al. (Nilsson, Blombäck & von Francken 1957, Nilsson, Blombäck, Thilén & von Francken 1959). The plasma of patients with von Willebrand's disease was assayed at dilutions 1:20, 1:50 and 1:100.

As 100 % standard for the assay of AHF in the patients use was made of mixed citrated plasma from 10–20 normal subjects collected at about the same time (at most an interval of 5 days) as the test specimen.

Normal values in 20 healthy men and women aged 20–40 years ranged from 60 to 160 % with a mean of 100 ± 17.5 %. The AHF-content in a group of 10 healthy women past the menopause ranged from 76 to 199 % with a mean of 139 %.

The mean error of the method at different AHF levels had been determined.

Table I
Mean error at different AHF-levels

AHF-level (%)	Standard error
0,1 – 1	± 0,1 – ± 0,3
2 – 3	± 0,6
4 – 6	± 1.4
15 – 25	± 4,5
30 – 40	± 5,-

Bleeding time

This was determined by

1) The method of Duke using standardised haemolets (Dade Reagent, Inc. Miami, Florida, U.S.A.). Determinations were mostly performed on both ears. Normal range 1 to 5 minutes.

2) The method of Ivy (Ivy Nelson & Bocher 1941), as modified by Borchgrevink and Waaler (1958) and also described by Nilsson, Magnusson and Borchgrevink (1963). An arm cuff was wrapped round the upper arm and inflated to 40 mm Hg. Three transverse incisions, 1 mm deep and 10 – 14 mm long, were made on the volar side of the forearm with a surgical blade (Gilette Surgical Blade E). The blood shed was gently and carefully absorbed at about 15 second intervals with a filter paper until the bleeding stopped. The mean of triple determinations in 35 volunteers examined at the coagulation laboratory in Malmö was 9.5 minutes (range 5 – 15.5 minutes) and in a later investigation (Cronberg 1968) of 70 volunteers 10.0 minutes (range 5 – 20 min.), S.D ± 3.1 and standard error ± 0.37. The bleeding time exceeded 15 minutes in 2 out of the 70 persons.

The corresponding mean found in Stockholm was somewhat lower and the bleeding time in normal persons did not exceed 12 minutes.

Platelet adhesiveness

The original method of Salzman (1963) was used with thin needle (caliber 0.14 – 0.2). Fresh blood was drawn directly from vein through a short column (11 – 13 cm) of glass beads into a vacuum tube with EDTA. The tube should be filled with about 5 ml in 40 – 50 seconds. Normal value according to Salzman 20 – 60. The normal value at the coagulation laboratory in Malmö based on 34 volunteers, aged 20 – 30 years, is 33 with S.D. ± 17.0 and standard error ± 2.9.

At estimation of platelet adhesiveness the platelets were counted with macro-method. For this purpose Hellem's modification (Hellem 1960) of Nygaard's method (Nygaard 1933) or Björkman's method (1959) were used.

Other tests

Other tests concerning bleeding and coagulation-status on persons included in the present investigation are listed below.

Coagulation time in glass tubes. Modified method of Hedenius (1936).

Coagulation time in plastic tubes, measured in the way described by Cronberg (1968).

Recalcification time of plasma (Nilsson et al. 1962).

Platelet counts (Kristensson 1928 – 29 or Björkman 1959).

Haemophilia B – factor (= FIX) (Nilsson et al. 1962).

Prothrombin consumption test (Biggs and Macfarlane 1957).

Prothrombin + factor VII + factor X. The P & P method of Owren and Aas (1951).

Factor V (Wolf 1953).

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Platelet aggregation, measured in the way described by Karaca and Nilsson 1972.

Platelet factor 3, measured in the way described by Karaca and Nilsson 1972.

AHF-CONCENTRATES FOR TREATMENT

For treatment with AHF-concentrates human Fraction I – O containing AHF prepared by the glycine method of Blombäck, B. and Blombäck, M. was used.

The preparations were originally made at Karolinska Institutet, and every batch was made from 1.400 – 1.600 ml of fresh plasma, obtained from 8 blood donors. This yielded about 3 g. of Fraction I – 0, which was dissolved in two bottles of 100 ml (100 ml = 1 dose of AHF). This preparation had an activity of 5 – 8 times that in normal plasma. The purification of AHF per mg protein in Fraction I – O

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RESULTS

The results are given in tabular form, (Table), where each family is described separately. The table contains data on the histories and values for the bleeding times according to Duke and Ivy, AHF-content in the blood and platelet adhesiveness according to Salzman. Other results of the bleeding and coagulation status did not show any remarkable deviation from normal. Only in single cases was the platelet count decreased or was a circulating anticoagulant demonstrated. This was then given in the column for remarks.

The Case reports (page 58) describe the most pronounced bleeding symptoms and those referred to in the text in order to illustrate their character and severity. When possible data are also given on the patient's age at the time of such bleedings.

A pedigree is given for each family.

Abbreviations

The following abbreviations were used in the tables:

Sex

M	– male
F	– female

Type

	– severe von Willebrand's disease (see page 13)
Mi	– mild von Willebrand's disease (see page 13)
Int	– intermediate results (see page 13)
N	– normal (see page 13)

When the severity of the disease could be judged only from the patient's history the classification is given in brackets: (Sv), (M) (Int).

Bleeding symptoms

In captions

N	– nose-bleeding
G	– gingival bleeding
TS	– tooth shedding with haemorrhage
TO	– traumatic oral or lip-bleeding
T	– tonsillar or pharyngeal bleeding
E	– ear bleeding
GI	– gastro-intestinal bleeding (not bleeding from haemorrhoids)
UT	– bleeding from urinary tract
M	– menorrhagia or metrorrhagia
Part.	– bleeding at parturition
O	– ovary bleeding
EH	– ecchymoses or haematomas
P	– petechiae
Tr	– *traumatic bleeding, even from* trivial cuts and injuries (traumatic oral or lip-bleeding and *intracranial bleeding excepted)*
J	– joint bleeding
TE	– bleeding after tooth extraction
Misc	– miscellaneous
Op.	– postoperative bleeding
Sum	– estimated general bleeding tendency

Miscellanous

Boil	– bleeding from boil
Ceph haem	– cephalic haematoma
Coit	– coital bleeding
Dent absc	– bleeding from dental abscess
Eye	– eye bleeding
FL o m	– bleeding in floor of mouth
Fract	– bleeding from fracture
Haemorrh	– bleeding from haemorrhoids
Hpt	– haemoptysis
Icr	– intracranial bleeding
I m	– intramuscular or deep subcutaneous bleeding
Max	– maxillary bleeding
Miscarr	– bleeding at miscarriage
Oes	– oesophageal bleeding
Pl	– intrapleural bleeding
Subarachn	– subarachnoid bleeding
Tooth erupt	– *bleeding at tooth eruption*
Umbil	– umbilical bleeding
Vag	– vaginal bleeding (menstruation and metrorrhagia excepted)

Operations

Ab	– abortion
Abd	– explorative abdominal operation
App	– appendectomy
Chol	– cholecystectomy
Curett	– uterine curettage

Dent. absc	–	operation of dental abscess
Ear	–	otological operation
Ex. ut	–	operation of extra-uterine pregnancy
Fract	–	operation of fracture
Fren. ling	–	operation of frenulum linguae
Gastr	–	gastric operation
Gyn	–	small gynaecological operation
Haemorrh	–	operation of haemorrhoids
Hernia	–	operation of inguinal hernia
Hy	–	hysterectomy
Icr	–	intracranial operation
Intest	–	operation of intestine
Joint	–	operation or puncture of joint
Lipoma	–	operation of lipoma
Lymph node	–	lymph node biopsy
Mam	–	operation of mammae
Max	–	puncture of maxillary sinus
Meato	–	meatotomy
Myom	–	myomectomy
Nose	–	nasal operation
Oes	–	operation of oesophagus
Ov	–	operation of ovary
Pimpl	–	incision of pimples
Pl	–	pleural puncture or thoracocentesis
Prost	–	prostatectomy
Salp	–	salpingectomy
Sect. caes	–	sectio caesarea
Skin	–	skin operation
Skin trapl	–	skin transplantation
Tartar	–	removal of tartar
Thyr	–	subtotal thyreoidectomy
To	–	tonsillectomy
Trach	–	tracheostomy
Vacc. scar	–	operation of vaccination scar
Veg. ad	–	removal of adenoid vegetations
Vertebr	–	operation of intervertebral hernia
Ves. stone	–	operation because of vesical stone
Wart	–	extirpation of wart

Grading of bleeding symptoms

The bleeding symptoms in the tables are graded according to severity as 1, 2 or 3. These signs denote essentially as follows:

1 Bleedings, which appeared to be more pronounced than in normal persons but were not severe or otherwise remarkable. They did not require any special measure and did not cause known anaemia.

Example:

Profuse or recurrent nose bleeding. No measures. Profuse or regularly recurrent gingival bleeding during toothbrushing. – Mild spontaneous gingival bleeding.

Profuse menstrual bleedings for a long time. No known anaemia. No treatment.

Bleeding at or after delivery described by patient as profuse. No data on amount of blood lost. No known anaemia. No treatment apart from routine methergin-injection at expulsion of the foetal head.

Bruises after trivial or unknown trauma.

Profuse or prolonged bleeding from small wounds. No treatment.

Profuse bleeding after tooth extraction. No treatment.

Profuse postoperative bleeding, reported with certainty by patient but not mentioned in hospital records.

2 Bleeding symptoms which were severe or otherwise remarkable or which required special haemostatic measures. They often caused anaemia. No blood transfusions given.

Example:

Nose bleeding treated with cauterisation or tamponade.

Spontaneous gingival bleeding when patient awoke in the morning with blood on pillow

Gastro-intestinal bleeding with considerable blood loss, often with demonstrable anaemia.

Abundant or prolonged urinary tract bleeding. Gross haematuria of unknown cause.

Profuse menstrual bleeding for which patient sought medical advice and treatment. Anaemia usually demonstrated.

Bleeding at delivery with loss of more than 600 ml blood or with demonstrated anaemia (not demonstrable before parturition) or which required special haemostatic measures.

Ovarian bleeding with very probable diagnosis.

Large or numerous haematomas for which patient sought medical advice and sometimes received treatment.

Traumatic bleeding, abnormally profuse for nature of injury and requiring special haemostatic measures.

Joint bleeding with very probable diagnosis.

Bleeding after tooth extraction which required treatment, e.g. suture or tamponade

Bleeding at or after operation which was noted in the records as remarkable

3 Bleeding requiring blood transfusion or being the cause of the patient's death, which is then stated in column for remarks.

The grading of the bleeding is, of course only approximate. Many factors were involved of which mention might be made of the following:

Evaluation depended largely on the patient's subjective opinion. Several data on the unexamined relatives of the probands were obtained from a third person. The occurrence of treatment often decided the evaluation of the severity of bleeding. It is however obvious that formerly patients sought medical advice much less often than nowadays and the indications for treatment vary from one physician to another. Anaemia, when reported, was confirmed by data on the Hb, but determination of Hb has many inherent sources of error and depends on the widely varying precision with which it is determined. – Reported blood transfusions could almost always be confirmed by examination of the records. The number of blood transfusions is naturally not a very reliable measure of the severity of bleeding, but it is not without value.

Other signs

Other signs used in the columns for bleeding symptoms were

This sign has been used at deliveries, miscarriages, fractures, tooth extractions and operations, which have occurred or been performed without abnormal bleeding

0 This sign has been used

a) in column for parturition regarding females above 15 years, who reported that they had never been delivered

b) in column for tooth extractions regarding patients in whom no tooth extraction had been performed

t This sign was used when specific therapy or prophylaxis had been given with fresh plasma and/or Fraction I – O. *t* before figures denotes prophylaxis and *t* after figures denotes treatment of bleedings.

Examination values

In columns for laboratory values the abnormal values for bleeding times, AHF and platelet adhesiveness according to Salzman are given in italics.

The following values were regarded as abnormal:

Bleeding time according to Duke	> 5 minutes
Bleeding time according to Ivy	> 15 minutes
Bleeding time according to Ivy in Stockholm	> 12 minutes
AHF	< 65
AHF in menopausal women	< 75
Platelet adhesiveness according to Salzman	< 20

s When the bleeding time according to Ivy was determined in Stockholm it is marked with s.

o When samples for determination of AHF were sent to the coagulation laboratory from another place for examination this is denoted by o

The menopause is noted when it was thought to be of particular interest, especially for classification of the person as affected, "intermediate" or normal (higher normal value for AHF in women in the menopause)

Table 2　　Abbreviations and signs explained on page 14–16

Family 1

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part	O	EH	P	Tr	J	Musc	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
													Bleeding history										Examinations					
V:5 BT	F	1939	S	3	3					3r		3	0		2		1	2		3	Gastr i	+++	5/56	>60		1–3		
																				i3	Hy i 2		6/56	>30		4		
																				i-	Curett 2		10/57	>60		4		
																							10/67	>30				
																							10/68				7	
III 5 EK	F	1898	Sv	2	1							2	0		1		1			1	Curett ?	+++	4/39	>90*				test. t lo-cal hosp.
																				i-	Skan i		4 39	7*				
																							4/39	>60*				
																							56	>30		5		
																										10		
IV 7 OJ	M	1893	MI							3		2								1	Curett	+	56	3		55		
IV 9 ST	F	1899	M																			+	56	6		62		
IV:15 OJ	M	1915	MI	1																		–	56	2		48		
IV 6 HJ	F	1892	Int.																				56	15		>100		
IV 5 KAT	M	1894	N																			–	56	1		86		
IV 8 EB	F	1897	N																			–	56	5		100		
IV 10 KJ	M	1901	N																			–	56	8		90		
IV 11 EJ	M	1904	N																			–	56	4		100		
IV 14 AA	F	1911	N												1								54	7		100		
V 3 KB	F	1931	N																			–	56	3				

Table 2 (continued)

Family 2

				Bleeding history																			Examinations					
Case	Sex	Born	Type	N	G	TS	TO	T	E	OI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sem.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III 2 YL	F	1941	S	3			1			2		3	15	3	1		3			1	Ov3	+++	8/56	>60		3		
																					Ov13		8/61	>60		4		
																							6/63	22	>30 s	20		Mens VIII
																							9/65	19		3		
																							10/65	14		2		
III 3 OL	F	1950	Sv	1		2	3	3r				3r	0							0		+++	56	>60		3		
																							56			4		
II 5 WM	M	1899	MI	1																		–	56	1		21		
II 11 HN	F	1907	M	1	1								1		1			1				+	56	4		32		
																							12/64	2	16	84		Menopau
II 14 KM	M	1911	MI																				56	1		21		
II 15 TM	M	1911	MI																			–	56	4 7		21		
II 16 IL	F	1914	MI																			–	8/56	3		37		
																							9/56	4				
III 1 ORK	M	1946	MI	1	1																	+	56	8		75		
III 5 ML	F	1924	MI	1	1										1	1						+	58	2		32		
III 13 LM	M	1941	MI		1															0			58	3		33		
III 10 PN	M	1936	Int.	1																		–	58	3		59		
I 1 FPL	M	1890	N																			–	56	1		104		
I 2 FL	F	1885	N																			–	56	5		87		
II 2 KL	M	1914	N																			–	56	3		85		
II 3 RDK	F	1917	N																			–	56	1		80		
II 4 HM	M	1897	N																			–	56	4		89		
II 7 FM	M	1902	N																			–	56	2		90		
II 9 SM	M	1904	N																			–	56	3		95		
II 10 JM	M	1905	N																			–	56	3		85		
II 13 MM	F	1909	N										0									–	56	7 10		95		
II 18 MM	F	1916	N												1							–	56	4		93		
III 6 KM	M	1928	N																			–	58	2		170		
III 7 IG	F	1929	N												1							–	58	3		120		
III 8 TBS	F	1931	N																			–	58	3		116		
III 9 BH	F	1931	N									1										–	58	3		132		
III 11 RM	F	1935	N																			–	58	2		88		
III 12 BM	F	1943	N																			–	58	3		115		
III 14 OM	F	1947	N																			–	58	4		70		

Table 2 (continued)

Family 3

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TB	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
												Bleeding history											Examinations					
III:1 MH	F	1930	Sv	3	2r	2	2	3		3		3	0		2				Coit 2	2		+++	9/56	>25		6		
																							9/56			14		
																							10/68	>30	>30		12	
II:9 MH	F	1905	M														1			1		+	56	4		48		
II:3 RS	F	1890	N																			−	56	3		94		
II:4 NH	M	1894	N																			−	56	4		100		
II:6 SH	M	1895	N																			−	56	2		100		
II:7 EH	F	1900	N																			−	56	10		86		
II:8 AH	M	1902	N																			−	56	1		90		
III:2 KH	F	1902	N																			−	56	9		98		

Family 4

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	T	J	Misc.	TB	Op	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
												Bleeding history											Examinations					
IV:1 GB	F	1940	S	1	3	2	3			3		3	0		2		3	3	Vag 2	3		+++	11/56	>60		5		fatal
																			Icr 3*	13			2/57	>60		5		
																							1/61	60		4		
IV:2 AB	F	1943	Sv	3	3		3											2	Boil 2	3	Pimpl 2	+++	43-	>10*				f tal
																							51	>15				** test at local hosp.
III:3 AB	F	1912	Mi																Mis-carr		Gyn I	−	12/56	1		45		
																					Curett							
III:5 NAH	M	1905	Mi																			−	12/56	4		43		
III:6 KB	F	1914	Mi																			−	12/56	7		53		
IV:4 YH	F	1944	Mi	1											1							+	1/59	6		46		
IV:5 TH	M	1947	Mi																			−	12/56	3		33		
IV:7 LB	M	1939	Mi																			−		3		38		
II:6 AH	M	1873	Int.																			−	12/56	4		56		
II:5 SH	F	1881	N																			−	12/56	2		128		
III:1 DD	F	1912	N																			−	12/56	2		98		
III:2 SB	M	1904	N																			−	12/56	10		95		
																							9/69	2 1	8			
IV:3 HCB	M	1948	N																			−	12/54	2		106		
IV:6 CH	M	1948	N																			−	12/56	6		98		
IV:8 AMB	F	1941	N																			−	12/56	6		107		
IV:9 HB	M	1945	N																			−	12/56	4		86		

 Table 2 (continued)

Family 5

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part	O	EH	P	Tr	J	Misc	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF	Sz	Remark
			Bleeding history																				Examinations					
IV 1 WP	M	1947	Mi	3	1										1		1			2		+ +	1/57 10/60 12/66	4 10 > 40 16	 21	15 47 79	 6	
II 8 EP	F	1887	M																	1		–	57	1		33		
III 1 EP	M	1910	Mi							2												+	57	5		42		
III 2 AB	F	1912	Mi	1	1																	+	57	2		52		
III 5 PP	M	1919	M	1											1	1				1	Lipoma 2 Myelography 1	+ +	1/57 10 60 12/66	> 30 43 3 2	 5	25 3 21	 9	
III 6 KS	F	1922	Mi																Miscarr			–	57			31		
III 8 MBP	F	1927	M										0									–	57	1		45		
II 1 PP	M	1881	N																			–	57	1		150		
II WJ	F	1880	N																			–	57	1		150		
III 3 EF	F	1914	N																			–	57			118		
III 4 EB	F	1917	N									3										–	57	1		180		Rupture myoma
III 9 BP	F	1930	N																			–	57	2		75		
III 10 MLj	F	1897	N																			–	57	5		150		
III 17 JP	F	1920	N																			–	57	3		76		

Family 6

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part	O	EH	P	Tr	J	Misc.	TE	Op.	Sum	Date m/year	Duke min.	Ivy min.	AHF	Sz	Remarks
			Bleeding history																				Examinations					
IV 2 RF	M	1955	S	2	2	2r	3								2		3r	2r	1.m. 2r	3 r-		+ + +	1/57 9 67 9 69	> 40		3 17 6	 10	
II 16 FOK	M	1888	Mi	1																	Prost 2	+	2/57	9		38		
III 2 MO	F	1918	Mi										0								App Hy Ov + Myom 3 Curett	+	2/57	2		43		

Table 2 (continued)

Family 6 (continued)

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min	AHF %	Sz %	Remarks
Bleeding history																						Examinations						
III 3 GS	F	1921	M										0							2		–	2/57	1		42		
III 5 KFK	M	1924	M																			–	2/57	4		34		
III. 6 EF	F	1930	M												1						Curett	–	2/57	2		23		
I. 4 SK	F	1884	N																			–	2/57	2		93		
II 1 SF	M	1901	N																			–	2/57	1		143		
II. 3 TF	M	1909	N																			–	2/57	2		90		
II. 5 OF	F	1905	N																			–	2/57	4		78		
II 7 NEK	M	1908	N																			–	2/57	2		79		
II 8 ÅK	M	1912	N																			–	2/57	1		74		
II 9 HK	M	1914	N																			–	2/57	2		132		
II. 11 HK	M	1925	N																			–	2/57	2		105		
II: 22 AMK	F	1886	N																			–	2/57	1		87		
II. 23 EK	F?	1888	N																			–	2/57	5		97		
III 1 YF	M	1925	N		1																	–	2/57	2		88		
III. 4 EB	F	1922	N																			–	2/57	5		104		
IV 1 EF	M	1948	N																			–	2/57	2		75		
IV 4 HB	M	1952	N																			–	2/57	5		103		

Family 7

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min	Ivy min	AHF	Sz	Remarks
Bleeding history																						Examinations						
III: 1 MA	F	1943	Sv	3	3	3	3		2	3	3r	3	0	2r	1	1	1	2	Tooth-erupt 2 Ceph haem 1 Icr 2 Fract	1	Icr 3	+ + +	3/57	> 40		4		under protection of fresh blood.
																										6		
																							2/59	>60 >60		4		
																							5/62		>60 s			
II: 1 OA	M	1916	MI	1	1										1				PI 2	1		+	57	1		27		
I 4 HSN	F	1882	MI	1								1	1				1					+		6				test t local hosp
II. 4 EA	F	1970	N																			–	57	2		146		

 Table 2 (continued)

Family 8

Case	Sex	Born	Type	Bleeding history N	G	TS	TO	T	E	GI	UT	M	Part	O	EH	P	Tr	J	Misc.	TE	Op	Sam.	Examinations Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
IIk 1 RB	M	1926	S	3	3		2			3	3				2	1	1	3r	Tooth-erupt 3 I.m. 1	3 r-	F bromo 2	+++	5/42	>60*				test at local hosp.
																							4/43	4*				
																							8/52	>30*				
																							3/57	>60		4		
																							3/57			10		
																							6/61		6			
																							11/61			6		
																							11/68			3		
I 2 EB	F	1899	MI	1								2										+	11/69	1 3	13	68		Menopaus
I 1 GB	M	1893	N																			–	11/69	2 3	11	105		
III 1 AMB	F	1953	N																			–	3/57	1		95		

Family 9

Case	Sex	Born	Type	Bleeding history N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sam.	Examinations Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
IIk 1 ES	F	1938	Sv					2		3r	2	2	0	3	1		1	2r	I.m. 1	2 r3	Skin r	+++	51	> 30				
																							7/57	>240				
																							3/59	> 60		3		
																							10/62			5		
																							1/64			4		
																							1/68	> 30	>30	3	6	
II 11 GvS	M	1928	MI																			–	57	6		43		
II 7 KS	F	1913	Int.																			–	57	3		33		
																							10/62	3		56		
I 4 EvS	F	1890	N																				5/67	1	10	100	52	Menopaus
II 4 PS	M	1910	N																			–	57	1		80		
II 8 MB	F	1915	N									1	0		1							–	57	4		123		
II 9 BE	F	1918	N																			–	57	3		69		
III 2 LS	M	1941	N																			–	5/67	1	15	85		
III 3 GS	F	1945	N																			–	5/67	1	8	95		
																							57	3				

Table 2 (continued) *Family 10*

Case	Sex	Born	Type	Bleeding history: N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Examinations: Date m/year	Duke min.	Ivy min.	AHF %	Sx %	Remarks
III: 1 MCA	F	1932	Sv	3	1		2			3r		3	0	3r	1	1	1		Pl 3	2	Curett 3	+++	9/55	>30				
																				r	Pl r		7/57	>60		17*		pleurisy
																							7/60	>60		4		
																							1/62	>30	>30	5		
																							11/64			4		
																							5/67	>30		8		
																							9/67				0	
II: 3 KN	F	1902	N										0									–	5/67	4 6	13	75*		Menopause
II: 8 VS	F	1905	N																			–	5/67	1	10	90*		
III: 2 GS	F	1933	N																			–	5/67	2	13	97*		
III: 3 DA	F	1940	N																			–	5/67	3	12	65*		
III: 4 BGS	M	1942	N																			–	5/67	2	9	65		
IV: 1 HS	F	1962	N																			–	68	3	8	102		

Family 11

Case	Sex	Born	Type	Bleeding history: N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Examinations: Date m/year	Duke min.	Ivy min.	AHF %	Sx %	Remarks
II: 1 GH	M	1913	B	1	2		2			3r					1	1	1		Hpt 2	2	Max 2	+++	12/57	40		10		
																					Abd / 3		4/65	>30				
																					Intest r		11/65			30		
																							11/65			17		
																							12/65			19		
																							11/66				3	
																							3/67	>30			3	

Family 12

Case	Sex	Born	Type	Bleeding history: N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Examinations: Date m/year	Duke min.	Ivy min.	AHF	Sx	Remarks
IV: 2 KPA	F	1948	Sv	3r	1		3			3		3	0		1		1	2		r1		+++	9/49	>30				
																							10/57	>60		3		
																							2/58	7 5		4		
																							2/58	58 42		5		
																							7/58	>60 >60		5		
																							1/68	~20 >70	>30	17	1 18	
																							5/68			5	6 13	
																							6/68			6		
III: 2 AA	F	1914	MI	2								1									Chol	+	10/57	5		59		
																							10/57			63		
IV: 3 KP	M	1952	MI																			–	10/57	4		38		
																							10/57			36		
III: 1 ML	M	1916	(I I)	1																								

Table 2 (continued)

Family 13

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sum.	Date m/year	Duke min	Ivy min.	AHF	Sz	Remark
																										Examinations		
								Bleeding history																				
III 2 BE	M	1935	S	3	1			3	2		2r				1	1	1		I m. 1	3	Ear 3	+++	10/57			8		
																				r3			5/59	36		8		
																				r-			10,68				31	
III 3 JIE	M	1945	S	1	1			3							1				Icr 3*	1		+++	3/59	11 .8		5		fatal
																				r-			4/59	7 120		2		
II 11 EE	F	1910	M	2								2			1					1		+	5/59	4		110		Menopaus
																							6,67	2	70	85		
II 10 AE	M	1910	N																			–	6 67	3	13	90		
III 1 DW	F	1933	N																			–	5/59	0 2		155		
III 4 LE	F	1947	N																			–	4/59	2		76		
																							10 65	2		74		

Family 14

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	T	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF	Sz	Remark
																										Examinations		
								Bleeding history																				
III 4 LJ	M	1957	MI	3	1													2		0		+	5 60	70 12		10		
																							6 65	2 6	>30	45		
																							11/66	2	70	35	0	
I 1 JJ	M	1881	(MI)	1																								
II 3 BJ	M	1911	Mi	2	2										1		1		Ocs 2	1	Ocs 1	++	46	6				test at local hosp.
																					PI 3		9 57	6				
																							6 65	2	>30	35		
																							11 66	2	>30	79	0	
III 1 SC	M	1937	MI	1																		+	11/66	2	10	33		
																							11/67	3 1	9	39	9	
III 2 GJ	M	1941	Mi	2			2								1					3		++	12,63	8 10	>30	32		
																				r-			5 64	5	78	19		
III 3 GJ	M	1943	MI	2	1					1					1		1			2	App intest	+	11/66	6 >30	>30	28	0	
II 1 NJ	M	1902	N	1																		–	11/66	1 1	11	95	79	
II 2 KAB	M	1909	N																			–	11'66	1	8	13	6	
II 4 LJ	F	1916	N																			–	5 60	2		100		
II 5 EJ	M	1913	N	1																		–	11'66	1 4	9	108	71	
II 6 GJ	M	1915	N	1																		–	11 66	1 3	13	90	41	
																							7 68	1 1	14	168	48	

Table (continued)

Family 15

Case	Sex	Born	Type	N	O	TS	TO	T	E	GI	UT	M	Part	O	EH	P	T	J	Misc	TE	Op	Sum	Date m/yrs	Duke min.	Ivy min.	AHF	Sz	Remark
II 4 KS	M	1934	M								2									r		+ +	10/62	1 5		90		
																							11/62	5 7	35	45		
																							12/62	2 4	37	44		
																							11/66		14	47	52	
																							11/66	1 2	15			
I BS	F	1897	N										1										11/66	2 2	11	123	60	
I 1 SS	M	1897	N																				11/66	2 2	25	125		
II 1 RL	F	1924	N									1	1										11/69	3	14	117		
II 2 TS	M	1928	N																				11/66	1 1	15	73	39	
II 3 GS	M	1931	N																				11/66	1 1	12	98	79	

Family 16

Case	Sex	Born	Type	N	O	TS	TO	T	E	GI	UT	M	Part	O	EH	P	Tr	J	Misc	TE	Op	Sum	Date m/yrs	Duke m	Ivy min.	AHF	Sz	Remark
III 1 AKZ	F	1946	S	3r	3	3					1	3r	0	2r	2			2	Fl m 2r Retro-per 2	3	Hy/3		58	60		4		Anti-AHF shown
																							6/61	~60				
																							1/64			3		
																							11/64		45	4		
																							1/67				0	
II LZ	F	1936	Mi	1																			3/60	3 5		55		
																							11/62	6	12s	75		
																							2/63			59		
																							1/67	2	16	67		
																										45		
III 3 ASZ	F	1959	Im																				1/67	2 2		53	46	
I 1 PL	M	1895	N																				11/62	6 4	5s	135		
III 2 MZ	F	1952	N																				1/67	2	14	85	76	

 Table 2 (continued)

Family 17

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
													Bleeding history												Examinations			
IV 5 LL	M	1926	Mi	2																1	Veg. ad.	+	3/62	2 1	40	48		
																							3/62	2 3		41		
IV 1 EL	M	1909	(S)	1			2		1		1						1	2		2								
II 6 KL	F	1863	(M)	1															Hpt 3*									fatal
III 2 HL	M	1884	(M)	1																								
III 3 JL	M	1886	(Mi)	1																								
III 4 AL	F	1891	(Mi)																Hpt 3									fatal
III 7 NL	M	1902	(Mi)	1																								
III 9 AL	F	1891	N																			–	5/67	4	9			
IV 2 MB	F	1917	N												1							–	5/67	1 4	15	135	21	

Family 18

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz	Remarks
													Bleeding history												Examinations			
II 1 VÅ	F	1924	Mi	2	1							2	3				1			1	To 2	+ +	10/58	4 5				
																					Chol 3		10/58	>60 11		4		
																							11 62	>30	>30	33		
I 2 AH	F	1898	Int.	2																	Chol	+	5/67	1 5	15	85		Menopaus
II 3 GH	M	1928	Int.	2																1		+	5/67	3 1	8	90*	4	
																							11/67	1 1	11	85	26	
II 4 ÅH	M	1931	Int.	2																		+	5/67	2 2	10	49	18	
																							11/67	4 5	12	100	30	
I 1 UH	M	1898	N																			–	5/67	1 1	7	95		
II 2 AH	M	1925	N																			–	6/67	3 3	9	90		
II 5 TH	M	1938	N																			–	5/67		7	45*	61	
																							11/67	3	6	85	52	
III 1 BÅ	M	1954	N																		Veg. ad	–	5/67	1 1		65		

Table 2 (continued)

Family 19

Case	Sex	Born	Type	N	G	TB	TO	T	E	GI	UT	M	Part	O	EII	P	Tr	J	Misc.	TE	Op	Sum.	Date m/year	Duke min.	Ivy min.	AHP %	Sz %	Remarks
			Bleeding history																				Examinations					
IIb 1 BA	F	1937	M	2	2	2					1	3	3							3	Ab 3 Curett 3	+++	1/57	7 4		94		
																							10/58	8 2		37		
																							5/67		>30	48		
																							6/70	5 5	24	78	22	
																							12/70	2	22	53	17	before inf
																								inf of 700 ml F I–0				
																												after inf
																									25	49	4	15 min.
																									21	94		6 hours
																									12	137		24 hours
II 2 JJ	M	1905	N																			–	5/67	2 0	10	140	73	
II 3 SJ	F	1908	N																			–	5/67	2 3	9	130	67	
III 2 AOB	F	1944	N																			–	11/67	5 5	11	98	12	
III 3 KJ	F	1951	N																			–	5/67	1 2	13	90	31	
IV 1 HA	M	1956	N																			–	5/67	4	20	70	0	

Family 20

Case	Sex	Born	Type	N	G	TB	TO	T	E	GI	UT	M	Part.	O	EII	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHP %	Sz %	Remarks
			Bleeding history																				Examinations					
IIb 1 GP	M	1909	MI	1	1					3										1		++	10/58	3 8*		46		large drops
																							11/68	5	12	35	59	
I 2 SP	F	1845	(MI)	1																								
II 1 AP	M	1872	(MI)	1																								
II 3 TP	M	1875	(MI)	1																								
II 5 PP	M	1879	(MI)	1	1																							
II 7 FP	M	1884	(MI)	1																								
IV 1 BOP	M	1939	MI		1			2							1					2	Lipoma 2	++	10/58	4 9*		17		large drops
																							11/68	~25	>25	30	9	
IV 2 KOP	M	1941	MI	3					2											3		++	10/58	3 7*		18		large drops
																							11/68		19	45	38	
III 2 SP	F	1906	N																			–	10/58	2 2		70		Menopause

Table 2 (continued)

Family I

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min	AHF	Sz %	Remarks
												Bleeding history											Examinations					
III 3 MÅ	F	1931	M									3	1		1			1		1	App	+ +	8/58	1 3		75		
																					Hy/2		10,58	11 1		32		
																					C rett		-/59			45		
																							6/59	3 2		40		
																							11/67	3 7	>30	90	10	
IV 3 OÅ	M	1953	Mi	2																	App	+	10/58	1 4		38		
																							5/68	3 3	17		10	
II 4 HS	F	1904	Int	2								2	2		1		1			2	App	+ +	10/58	5 1		67		
																							6/67		11	95		
III 1 SÅ	M	1926	N																			–	10/58	3 2		83		
III 2 SS	M	1929	N																				11'67	3 5	10	95	0	
IV 1 IÅ	F	1949	N																				10/58	3		83		
IV MÅ	F	1952	N																			–	10'58	3 4		120		

Famil

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sum.	Date m/year	Duke min.	Ivy min.	AHF	Sz	Remarks
												Bleeding history											Examinations					
III 1 ID	F	1943	Sv	3/	1	1	2					2	+	2	1	1	1	2		2		+ + +	3 59	76		15		
																							11 62	>60	8s			
																								60				
																							1 63			39		
																							5 65		14	61		mens VII
																							10 65	5				
																							-.66	8				
																							1 67	30	30			
																								>30				
I 2 II	F	1910	Int.	1																1		–	11'62	11 11	6	76		Menopaus
																							1 63		12	84		
I 1 HI	M	1909	N																				1 67	1 3	8	160		
II 2 CI	M	1947	N														1					–	1/67	1 3	12	95		

Table 2 (continued) *Family 23*

Case	Sex	Born	Type	N	O	TS	TO	T	E	OI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sam.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
				Bleeding history																			Examinations					
IIb 12 KW	F	1951	Sv	2	1		1	3r				3	0		2	1	1			2	T 1	+++	7/59	22 10		22		
																							8/59	35 > 60		6		
																							12/61	> 40	> 30	30		
II 4 SW	F	1921	S									3	0	3*	1					2	Ov 3*	+++	4/41	> 25**				dead fter op. ov 1941 test t local hosp
I: 2 AMW	F	1883	(M)	1																								
II. 1 JKW	M	1913	(M)	1																								
II. 2 SE	F	1916	(M)									1																
II 5 NW	M	1927	MI	1											1							+	7/59	2 2		2		
III 2 BW	M	1952	(MI)	1																								
III 7 BW	M	1953	(M)	1																								
II. 15 OW	F	1931	N												1							–	5/67	2 2	23*	100	24	insignificant bleeding
III 13 PW	M	1951	N																			–	5/67	1 5	10	65	43	

Family 4

Case	Sex	Born	Type	N	O	TS	TO	T	E	OI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sam.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
				Bleeding history																			Examinations					
IIb 1 RA	M	1942	S	2	2		2									1	1			r-	None Vacc.scar 1	++	9/59	49 18		16		
																										20		
																							2/62	19 > 30	> 30	38		
II 5 BA	F	1926	N																				5/67				18	
III 2 AMA	F	1947	N	2								1	0									–	5/67	1 2	9	105	10	
																						+	5/67	5 2	13	105		

Family 25

Case	Sex	Born	Type	N	O	TS	TO	T	E	OI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sam.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
				Bleeding history																			Examinations					
IV: 1 GL	F	1918	MI	1									3		1					2	Veg ad Icr 2 Hy 3	++	9/59	8 7		43		
IV 2 BW	F	1923	MI									1	0		1								9/59	9 4		42		
																						+	1/67	9 5	> 30	105		
III 2 MW	F	1889	(Int)	1																			5/68	2 3	17	65		
V 1 KL	F	1953	N																									
V 2 KL	F	1958	N																			–	4/66	4	5	85		
																							4/66			64		
																				1		–	4/66	5		58		
																							4/66		7	72		

8 *Table* (continued)

Family 6

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sx	Remarks
IIb 2 EF	F	1939	S	3			2	3					/3			1				2		+++	54	>60*				test at local hosp
																							9/59	>60		17		
																							2/65	11 18				mens IX
																							12/66	2 >60	>30			
II 4 WH	M	1909	Int																			–	12/66	2 2	12	45*		
																							12/67	2 1	7	40		
III 4 BR	F	1945	Int.									1			1					1	App	+	12/66	1 1	10	80	45	pregnant
II. 8 RH	F	1916	N												1							–	12/66	1 1	14	74		menopaus
III 1 BH	M	1938	N															17				–	12/66	2 3	12	55*	45	
III 3 SH	M	1943	N																			–	12/66	2 2	14	70*		
III 5 ILH	F	1949	N																			–	12/66	1 1	14	78*		
IV 1 PF	M	1965	N																			–	12/66	1				

Family 7

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sx	Remarks
IIb 4 KR	F	1921	S	2	1						1	3	0	3	1	1	1	2		2	Chol /3	+++	43	>50*				test at local hosp.
																					Curett 3		45	>90*				
																					Joint /		11/59	>60		5		
																							11/59			7		
																							11/64	>30		4		
III 2 ASS	F	1914	(Sv)	2	2								0										9'69				17	
III 3 GG	F	1917	Int.									1									Hy	–	6/67	11 5	14	95		dead 1979 of nephritis
II 3 RS	M	1892	N																			–	6/67	1 1	9	105*		
II. 9 ES	F	1893	N																			–	6/67	2 1	12			Menopaus
III. 1 AMN	F	1912	N																			–	6/67	1 1	12	80*		Menopaus
III 5 NES	M	1926	N												1							–	6/67	1 1	13	90*		
III 6 EMS	F	1931	N																			–	6/67	4 2		76		

Table 2 (continued) *Family 28*

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Stom.	Date m/year	Duke min.	Ivy min.	AHF %	Sx %	Remarks
													Bleeding history												Examinations			
II:4 AB	M	1915	MI	1	1					3										12 t-	App 1	++	11/59	10 6		23		
																					Chol t		11/59	9 4		16		
																					Mam 3		6/62	>30 4	>30	25		
																					Lymph. node t		6/64	2 2	21			
																							7/64	10 4	>30	27		
																							11/64	3 3	>30	33		
II. 1 HO	F	1908	MI	2								2								1	Curett	+	11/66	1 1	23	44	26	
II 6 UBK	F	1927	MI																			–	11/66	1 1	19	90	48	mens VI
																							11/68	15 9	12	48	67	
III: 2 IN	F	1939	MI		1					3		1	0		1		1			t-	Chol t	++	11/59	4 4		26		
																							11/59	8 3		27		
																							2/62	2 3	12	32		
																							2/62		18	125		
																							1/65			40		
																							1/67			115		
III: 3 AS	F	1947	MI										0									–	11/59	6 3		37		
																							12/59	9 10		43		
																							1/62	2 2	9			
II. 3 ML	F	1914	Int.	1								1			1							+	11/66	3 7	19	81	0	
																							11/66	2 1	19	110	14	
II. 2 AH	F	1912	N																			–	11/66	1 1	27*	97	58	deep incision
II 5 EP	F	1924	N										0								Ex ut 3	–	11/66	3 2	10	107	32	
III 1 SJ	F	1933	N																			–	11/68	5	11	82		

Family 29

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Stom.	Date m/year	Duke min.	Ivy min.	AHF %	Sx %	Remarks
													Bleeding history												Examinations			
III: 1 IGK	F	1926	MI	1								3	0		1	1	1			3	Ear 1	++	11/60	4 1		64		
																				t-	Ear t		6/62	5 3	22	39		
																					Trach t							
																					Ov		7/62	2 2	14	41		
																					Ex ut							
																							5/63	3 1	11	43		
																					Curett 1							
																					Skintrapl t 1							
III: 2 ÅW	F	1936	Int.		1								1									–	11/67	8 9	12	95	0	
III. 4 ÅH	M	1945	Int.	1																		–	11/67	1 1	5	60	17	
III. 3 BF	F	1940	N																			–	5/67	3 3	10	90*		

Table 2 (continued) *Family 30*

Case	Sex	Born	Type	N	O	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sam.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
											Bleeding history												Examinations					
III 2 AW	M	1951	M	2r											1		1					+	3/60	7 3		38		
																							12/60	6 3		70		
																							10/61	5 9		76		
																							9/62		15			
																							11/66				0	f tal
III 1 ÅW	M	1951	(Mi)	2*																		—	3/60	2 1		63		
II 4 EW	F	1931	Int																				9/62	2 3	9	6.		
III 3 PW	M	1956	N																			—	11/66	2 1	11	78	0	

Family 31

Case	Sex	Born	Type	N	O	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sam.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
											Bleeding history												Examinations					
II 4 LJ	F	1903	M	1							1	1			1	1			Haemorrh 1		Chol	+	1 60	4 9		7		
																					Chol / Haemorrh 3		1/60	8 3		5		
																							12/66		13	41	14	
III 2 AJ	M	1927	Mi	1													1			2	To 1	+	12/66	1 1	17	35	37	
III 1 GB	M	1923	N																			—	12/66	3 2	7	32	14	
																							6,68	2 3	11	77	79	
III 3 ME	F	1929	N	2									1	1							Chol	+	1./66	1 2	14	57		
																							11/68	4 3	14	95		

Family 3

Case	Sex	Born	Type	N	O	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sam.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
											Bleeding history												Examinations					
IV 1 AJ	F	1960	Sv	3	1	2	3			1					1	1		2r		2		+++	6'62	>45				
																							10'62	>50		17		
III 2 SN	F	1929	Mi																Mis-carr		To Curett	—	10,62	7 7	8s	58		
III 3 OA	M	1931	Mi																				9 62	3 4		45		
III 5 MJ	F	1937	Mi																Mis-carr		Curett	—	9'62	4 4	11s	49		large drops
																							9'62		2	54		
III 6 ÅA	M	1941	Mi																		Chol	—	9/62	7 5		41		
II 4 BA	M	1903	Int.																			—	9'62	4 4		53		large drops
II 7 CA	F	1902	N																			—	9'62	3		77		
III 1 BJ	M	1932	N																			—	9/62	4 4	16	87		
III 4 GB	F	1935	N																			—	10/62	7 4		100		

Table 2 (continued)

Family 33

Case	Sex	Born	Type	Bleeding history																		Sum.	Examinations					Remarks
				N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	T	J	Misc.	TE	Op.		Date m/year	Duke min.	Ivy min.	AHF %	Sz %	
IIh 2 AR	M	1942	Sv		2										1		3	2		3	Tartar 3	+++	10/62	>30	>30	19		
																								>30				
																							10/62	>30		19		
																				12	Tartar 1		5/63	5 >30		36		
																				1	Fren.ling 3	–	5/67	6 5	10	185*		
II: 8 SR	F	1897	N																									

Family 34

Case	Sex	Born	Type	Bleeding history																		Sum.	Examinations					Remarks
				N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	T	J	Misc.	TE	Op.		Date m/year	Duke min.	Ivy min.	AHF %	Sz %	
III: 1 SP	F	1914	MI	1	1					3		1			1	1	1			2		++	10/58	1 8*		63		large drops
																							11/58		12	45		
																							4/60	7 6		35		
																							10/62			78		
																							2/63	11	18s	88		
																							1/67	3 2	>30		9	
I 1 KL	M	1857	(MI)							3*																		fatal
II: 1 HP	F	1882	(M)							3*																		fatal
III 2 IL	M	1916	MI							3c*					1						Gastr 3	++	3/60	1 3		54		fatal
																							3/60	7 4		38		
																						+	5/67	8 15	18	67	0	
IV 3 IL	F	1944	M	2	1					1		2	0		1		1			2			1/68	9 8	28	63		
																							3/68	3 3	>30	60	25	
																							5/68	6 5	18	75		
																					Mam 2	+	12/67	1 1	>30	225*		
III: 3 BL	F	1918	Int.		1																	–	6/62	3		88		
IV 4 RL	M	1946	Int.																				5/67	3 5	~30			
																						–	11/67	1	7	95	18	
III 4 HL	M	1920	N																			–	11/67	5 5	13	175	24	
III. 5 IL	F	1924	N																			–	1/67	1 1	12		47	
IV 1 LP	M	1931	N																	2		+	4/67	5	5	96		
IV: 2 BL	M	1941	N		1																		4/67		10	107		
																							5/67		13		36	

Table 2 (continued) *Family 35*

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
										Bleeding history															Examinations			
IIb 4 PT	M	1905	M	1						3							1			2		++	3/60	4 11		16		Anti-AHF shown
																				12			4/60	5 3		17		
																				1			6/60	3 3		8		
																							1/62	6 3	15	12		
																							1/62		>30			
																							11/63	4 4		8		
																							11/64	3		11		
																							6/65			79		
II 10 DS	F	1915	MI	1	1					1							1		Mis-carr 1		App Ov Mam 1	+	12/66	4 3	16	83*	0	Menopaus
III 7 PT	M	1935	MI																			–	2/62	2 3	17	40		
																							2/62			53		
III 8 AT	M	1938	MI	1	1															1		+	2/61	6 5		31-		large drops
																							5/61	1 2		31		
III 21 GS	M	1946	MI	1																1		+	12/66	4 5	16	49*	25	
III 22 HS	F	1948	MI										0									–	12/66	1 2	18	65*	45	
III 23 SS	F	1949	MI	1									0									–	12/66	1 2	20	49*	44	
II 6 SC	F	1908	Int.		1							1										+	6/67	1 1	>30	125*		Menopaus
II 2 PT	M	1900	N														1					–	6/67	1	5	145*		
II 3 NT	M	1902	N																			–	1/67	1 2	9	110	76	
II 5 NL	F	1906	N																			–	1/67	1 1	19	85	27	
II 9 TP	F	1914	N																			–	6/67	2 3	11	85*		
III 6 LT	M	1934	N																			–	3/64	4 4	11	100		
III 9 ET	F	1941	N		1																	–	1/64	1 3	11	80		
III 10 SL	M	1936	N	1	1																To 1	+	11/67	2 2	10	185	38	
III 24 DS	F	1955	N	1																		–	12/66	1 2	9		30	

Family 36

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part	O	EH	P	Tr	J	Misc.	TE	Op	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
										Bleeding history															Examinations			
IV 2 IN	F	1948	S	3	1								13		1	1	1	1		1		+++	8/60	55 63		2		
																							6/66		>40s	2		
																							8/68	>30		5		mean IX fatal
III 19 KB	F	1904	(Sv)		1							3			1													
III 3 AN	M	1907	N																			–	6/67	2 2	8	75*		
III 13 MF	F	1911	N	1																	App	–	8/60	5 3		71		
																							6/67	1 1	9	105*		Menopaus
IV 1 LN	M	1946	N																			–	6/67	1 1	8	50*		
IV 3 AM	F	1941	N																			–	4/67	3 2	12	80*		

Table 2 (continued)

Family 38

Case	Sex	Born	Type	N	G	TS	TO	T	E	Gl	UT	M	Part.	O	EH	P	Tr	J	Misc.	TB	Op.	Sem.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
IV: 4 KS	F	1944	M	3	1							2	0		1	1				1	Veg ad 3	++	9/60	>60 23		26		
																				11	Curett		1/61			34		
																							2/61	14 10		32		
																							2/61	21 29		62		
																							1/68	8 7	18	27	10	
																							1/68		>30		19	
																							3/68	13 1	>30	18	14	Treated with p-pills
																							3/68				30	
																							7/68	6 6	>30	21	1	
IL 2 TO	F	1892	(M1)	1								1	1															
IL 3 IS	F	1921	M	1	1							2	2		1	1	1				To	+	1/61	8 14		36		
																					App							
																					Curett		5/67	1 5	26	45	5	
IL 7 EP	F	1924	MI	2								1	1				1		Hpt 1	1	Chol 1	+	3/67	4 2	18	70	9	
																					Curett							
IL 8 RS	F	1925	M	1											1					1	Curett	+	1/63	13 8	>30s	47		
																							1/67	1 2	>30	42	45	
IL 9 VS	F	1933	M1	1	1							1	1		1					1		+	1/63	12 9	12s	103		
																							1/67	2 1	24	80	25	
IL 10 SG	M	1934	M																		App	−	1/67	2 1	16	50	17	
IL 11 BS	F	1942	MI		1							3			1					2	Veg ad 3	++	6/67	2 4	>30	30		
																					Curett							
V 3 JES	M	1938	MI	2											1				Fract	1	Ear 2	++	9/60	7 14		14		
																							12/60	11		21		
																							11/62		>30			
V 6 JS	M	1947	MI	2																1		+	1/63	8 8	17s	76		
																							1/65	4	20s	39		
IL 1 MW	F	1913	N	1								1								2	App	+	6/67	3 2	12	110		
																					Ov							
II 2 RO	M	1917	N																			−	1/67	1 3	8	125	72	
II 4 ÅS	M	1916	N																			−	5/68	4 1	5	95	29	
V 8 JS	M	1958	N	2																		+	1/63	1	10s	160		
V 9 JS	M	1960	N																			−	3/63	4		108		

Table 2 (continued)

y 40

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sum	Dat m/year	Duk min.	Ivy m	AHF	Sz	Remarks
													Bleeding history												Examinations			
III 3 AMW	F	1956	Sv	3	1	3r	3	3r	1	1					2	1	2	2r	Tooth-erupt 1 Subcut 2r	1		+++	11/60	>20				
																							10/62			3		
																							11/62		>22s	4		
																							11/62			14		
																							11/68	>30			17	
																						++	1/63	14 8		135		fatal
I 2 GW	F	1891	M	2						3*																		
II 7 FW	M	1925	M	1													1			1		+	11/62	9 8	15s	73		
																							11/62	12 13	>30s	94		
																							11/68	16 4	>30	115	6	
																						−	8/69			50		
II 8 SW	M	1930	Int	1																		−	11/62	4 10	7s	90		
II 11 IW	F	1927	N									1										+	11/62	6 7	11s	120		hospitalized in June 1962 for thrombocytopenia
III 1 IW	F	1957	N							1					1		2		Im. 1				11/62	9	19s	123		

Family 41

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
													Bleeding history												Examinations			
II 1 ES	M	1892	MI	2						2							1			0	Chol App Prost 2	+	56	11*				test t local hosp
																							12/60	3 2		48		
																							5/61		15	53		
II 2 ES	M	1899	(MI)	1																								
II 4 ES	M	1903	(Mi)	1																		−	5/62	4 2	21	99		
III 1 BH	F	1924	Int.																			+	5/62	1	23	98		
IV 1 GH	M	1950	Int.	2																		−	5/62	2 2	16	88		
IV 2 TH	M	1953	N																									

Table 2 (continued) *Family 42*

Case	Sex	Born	Type	N	G	TS	TO	T	B	GI	UT	M	Part	O	EH	P	Tr	J	Misc.	TE	Op.	Sens.	Date m/year	Duke min.	Ivy min.	AHP %	Sz %	Remarks
												Bleeding history												Examinations				
IV 42 PS	M	1958	MI	2/			2								1					r-		++	10/62	8 15		21		
																							10/62	9 8		16		
																							8/67		>30	40	34	
I: 1 OA	M	1863	(MI)	1													1			1								
II: 1 EN	F	1888	(Mi)	1															Mis-carr 3	1								
II 2 GÅ	F	1891	(Mi)	2																								
II: 4 HN	F	1899	M	2	1								–		1		1			1	T 2	++	5/62	8 6	>30	43		
																							10/67		>30	40	2	
II 5 AS	F	1903	MI	1	1							2	1							2	Hy 3	++	5/62	2 1	>30	47		
																					Curett 2		8/67		>30	60	0	
II 7 IA	M	1906	MI	1													1					+	10/61	2 4	25	38		
																							5/62		>30	42		
																							8/67		20	45	1	
II: 8 NA	M	1908	M							3										2		++	5/62	2 2	>30	30		
II: 9 SP	F	1912	MI	1									2		1	1				2	Sect caes	+	5/62	15 24	>30	79		
																					Curett		8/67		20	55	2	
III 2 IN	M	1913	MI	2																1	App 2	+	10/62	3 3	30	48		
																							8/67		14	85	35	
III 3 MR	F	1917	MI									1										–	11/62	2	30	56		
III: 4 AF	F	1923	MI									2			1					2	Hy 3	++	5/62	5 3	>30	36		
																					Curett		8/67		>30	47	7	
III: 6 AGC	F	1921	MI	1			1					2	1		1						Curett 1	+	1/63	3 7	>30	30		
III 9 OÅ	M	1926	MI	1																2		+	10/62	3 4	>30	36		
III 10 KÅ	M	1928	MI												1					2		+	11/62	3 4	26	49		
III 13 IS	F	1936	MI												1							–	11/62	3 3	18	45		
III 19 IH	F	1918	MI	2	1							3/	2 2		1					2	Nose 1	+++	2/42	>18*				test t local hosp.
																					Hy t 3		12/42	>15*				mens III
																					Curett 3		1/43	3				mens IV
																					Pl 2		11/50	13*				
																							12/53	4				mens III
																							5/62	5 9	36	58		
III 20 BN	F	1923	MI	1									0				1		Hpt 1 Pl 2		Pl2 3	++	2/42	8*				test at local hosp ** fatal
III. 21 BN	M	1926	MI	1																1		+	5/62	3 5	23	49		
III 22 MP	F	1928	MI												1		1					–	5/62	4	25	33		
																							10/62			56		
																							8/67		>30	50	42	
III 24 IN	M	1935	MI	1																								

Table 2 (continued)

Family 40

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	[illegible]	M	P	[illegible]	LH	P	T	Misc.	TE	Op.	Date	Duke	Ivy min.	AHF	Sz	Remarks
III, 3 AMW	F	1956	Sv	3	1	3/	3	3/1		1					1	1	2	T subarach. I S brain 2/			11 [illegible]	[illegible]				
																					1			[illegible]		
																					1			4		
																					11			11		
																					1	10			17	
																					1 [illegible]	1 5		135		[illegible]
I. 2 GW	F	1891	MI	2						3																
II. 7 PW	M	1925	MI	1													1		1		11 6	9 [illegible]	15	73		
																					11 62	1 13	30	94		
																					11 68	15 4	30	115	6	
																					3 69			50		
II. 8 SW	M	1930	Int.	1								1									11 62	4 10	7[illegible]	90		
II. 11 IW	F	1927	N							1					1		2	1 m 1			11 6	6 7	11	170		hospitalized in june 1962 for thrombocytopenia
III. 1 IW	F	1957	N																		11 62	9	19	1 3		

Family 41

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sam.	Date m/year	Duke min.	Ivy min.	AHF %	Sz	Remarks
II. 1 ES	M	1892	MI	2						2							1			0	Chol App Prost 2	+	56	11				test at local hosp.
																							12/60	3 2		43		
																							5/61		15	53		
II. 2 ES	M	1899	(MI)	1																								
II. 4 ES	M	1903	(MI)	1																		–	5/62	4 2	21	99		
III. 1 BH	F	1924	Int.																			+	5/62	1	23	98		
IV. 1 OH	M	1950	Int.	2																		–	5/62	2 2	14	88		
IV. 2 TH	M	1953	N																									

Table 2 (continued) *Family 4*

Case	Sex	Born	Type	Bleeding history N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sem.	Date m/year	Duk min.	Examinations Ivy min.	AHF %	Sz %	Remarks
IV 62 PS	M	1958	Mi	2r			2								1					r		++	10/62	8 15		21		
																							10/62	9 8		16		
																							8/67		>30	40	34	
I 1 OA	M	1863	(Mi)	1																								
II 1 EN	F	1888	(M)	1													1			1								
II 2 GA	F	1891	(Mi)	2															Miscarr 3	1								
II 4 HN	F	1899	Mi	2	1								–		1		1			1	T 2	++	5/62	8 6	>30	43		
													–										10/67		>30	40		
II 5 AS	F	1903	Mi	1	1							2	1							2	Hy 3	++	5/62	2 1	>30	47		
																					Curett 2		8/67		>30	60	0	
II 7 IA	M	1906	Mi	1													1					+	10/61	2 4	25	32		
																							5/62		>30	4		
																							8/67		20	45	1	
II 8 NA	M	1908	M							3										2		++	5/62	2 2	~30	30		
II 9 EP	F	1912	Mi	1									2		1	1				2	Sect caes	+	5/62	15 14	>30	29		
																					Curett		8/67		20	55	2	
III 2 IN	M	1913	Mi	2																1	App 2	+	10/62	3 3	30	43		
																							8/67		14	85	35	
III 3 MR	F	1917	Mi									1										–	11/62	2	30	34		
III 4 AF	F	1923	Mi									2			1					2	Hy 3	++	5/62	5 3	>30	36		
																					Curett		8/67		>30	47	7	
III 6 AQC	F	1921	Mi	1			1					2	1		1						Curett 1	+	1/63	3 7	>30	30		
III 9 OA	M	1926	M	1																2		+	10/62	3 4	>30	36		
III 10 KA	M	1928	Mi												1					2		+	11/62	3 4	26	49		
III 13 IS	F	1936	M												1							–	11/62	3 3	28	45		
III 19 IH	F	1918	M	2	1							3r	2 2		1					2	Nose 1	+++	2/42	>18*				test at local hosp.
																					Hyr 3		12/42	>15*				mens III
																					C rett 3		1/43	3				mens IV
																					Pl 2		11/50	13*				
																							12/53	4				mens III
																							5/62	5 9	26	58		
III 20 BN	F	1923	Mi	1									0				1		Hpt 1 Pl 2		Pl2 3	++	4/42	8				test at local hosp. fatal
III 21 SN	M	1926	Mi	1																1		+	5/62	3 5	25	49		
III 22 MP	F	1928	Mi												1		1					–	5/62	4	23	53		
																							10/62			56		
III 24 IN	M	1935	Mi	1																			8/67		>30	30	42	
III 25 SN	F	1937	Mi	2	1										1		1			1		+	11/62	14 6	24	28		
												1	0		1		1	3		2	Joint 3	++	2/54	10*				test at local hosp.

Table 2 (Continued)

Family 42 (continued)

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part	O	EH	P	T	J	Misc	TE	Op	Sum	Date m/year	Duke min.	Ivy min.	AHF	Sz %	Remark
																							5/62	>30 10	>30	30		
																							8/67		>30	45	1	
III 26 EN	F	1940	Mi	2								1	0		1		1			1		+	5/62	9 9	>30	43		
																							1/67	2 5	>30	30	16	
																							9/67	6 ~30	>30	3	18	
III 27 KZ	F	1930	M	1	1								3		1		1			1		+ +	10/62	3 3	>30	42		
																							8/67		>30	40	12	
III 28 KB	F	1939	M	1																1	Gyn / Salp + pp[1]	+	10/62	2 3	>30	79		
III 31 IS	F	1932	Mi	1	1								2									+	11/62	4 3	4	44		
III 32 NOA	M	1934	M	2												1				2	App	+	11/62	5 4	>30	41		
																							8/67		>30	40	10	
III 33 BAA	M	1937	Mi	2	1										1				Ep 2r	2	App	+ +	12/61	3 2	4	38		
																							1/62	4 2	8	30		
																							8/67		21	45	1	
III 35 KS	F	1940	Mi	1								3			1		1			2		+ +	10/61	15 6		48		mens VI
																							5/62	1 8	>30	35		
																							8/67		>30	45	1	
																							10/68			35	7	
III 37 IBK	F	1934	Mi		1								2									+	5/62	4 3	30	36		
																							8/67		21	40	6	
III 39 JIA	M	1946	Mi																			–	11/62	3 2	>30	44		
																							8/67		16	45	6	
III 40 LA	F	1948	M	1	1							1	0							1	Veg ad 2	+	5/62	3 1	27	41		
																							8/67		2		0	
III 42 MP	F	1953	Mi									1	0			1					To	–	11/62	2 3	>30	55		
																							8/67		10	70	39	
IV 7 JEF	M	1949	Mi	2	1		1								1					1		+	5/62	2 8	5	48		
																							8/67		9	43	31	
IV 12 IC	F	1948	Mi	1	1	2						2	0		1	1	1			2		+ +	1/63	>30	>30	34		
IV 16 TÅ	M	1951	Mi	1																		–	10/62	2 3	>30	53		
IV 17 LÅ	F	1952	Mi																			–	10/62	1 2	>30	37		
IV 18 ChÅ	F	1956	Mi												1					1-		–	10/62	3 3	>30	31		
IV 24 BS	F	1958	Mi																	2		+	11/62	3 3		38		
IV 31 HIH	M	1940	Mi																	0		–	11/62	3 3	21	43		
IV 33 LH	M	1945	Mi														1			1		+	5/62	3 3	5	14		
IV 34 GH	M	1947	Mi		1															1-		–	11/62	3 3	25	43		
IV 39 JN	M	1959	Mi	2	2										1		2			1-			3/63	>30		49		
																							8/67		>30	40	0	
IV 44 MZ	M	1958	Mi	1																		+	10/62	4	>30	20		
																							8/67		8	40	9	
IV 45 AZ	F	1961	Mi												1		1			0		+	8/67		>30	38		
IV 46 ME	M	1958	Mi												1		2r			0		+	10/62	4	>15	79		

Table 2 (continued) Family 42(continued)

Case	Sex	Born	Type	Bleeding history: N	G	TS	TO	T	E	GI	UT	M	Part.	D	EH	P	Tr	J	Misc.	TE	Op.	Sem.	Examinations: Date m/year	Duke min.	Ivy min.	AJIF %	Sz %	Remarks
																						++	10/64	4		30		
IV: 47 HE	M	1961	MI	2																			10/64			37		
																						+	11/62	2	>30			
IV: 60 AA	M	1960	MI	1			1				2				1					1			8/67		>30	75	19	
																						+	8/67		>30	30	4	
IV: 61 GA	F	1963	MI	1											1		1			1		++	11/62	8				
IV: 63 BIS	F	1960	MI	2																			8/67		>30	45	0	
																						+	5/62	4 5	>30	32		
IV: 67 AK	M	1955	M												1					2		+	5/62	3 3	7	121		
III: 41 AIA	F	1943	Int.	1								2			1					1		+	11/62	2 1	16	80		
IV: 3 UR	F	1943	Int.										0							2		+	11/62	2 1		56		
IV: 25 CS	F	1959	Int.																			–	8/67		10	47	45	
IV: 38 MN	M	1956	Int.																			–	10/62	1 1	12	87		
II: 3 EA	M	1894	N																			–	5/62	1 1	9	82		
III: 1 NEN	M	1911	N																			–	1/63	5 3	12	143		
III: 5 MA	F	1919	N									1										–	1/63	7 4	9s	112		
III: 7 IP	F	1923	N								1				1							–	1/63	4 3	9	91		
III: 8 EA	F	1924	N																			–	10/62	3 5	17	85		
III: 11 SA	M	1929	N																			–	2/63	1 3		75		
III: 12 UL	F	1932	N																	1			4/63		15	82		
III: 14 GS	F	1927	N									1										–	10/62	3 3	15	71		
III: 15 EA	F	1930	N																				11/62	2 1	13	68		
III: 16 UU	F	1931	N										1									–	10/62	1 4	20	126		
III: 17 MA	F	1933	N																			–	11/62	3 1	11	73		
III: 18 LA	M	1941	N																				11/62	4 1	9	84		
III: 23 GR	F	1930	N																		Dent absc1		5/62	4 4	11	92		
III: 29 BK	F	1929	N																				11/62	1 2	17	119		
III: 30 BEA	M	1931	N																				11/62	2 3	9	64		
III: 34 NES	M	1937	N	1																		–	8/67		10	68		
III: 36 LA	M	1932	N	1	1																	+	4/63	1 3	14	83		
III: 38 SP	F	1935	N																				11/62	3 4	18	104		
IV: 6 BIF	M	1944	N																			–	5/62	3 3	8	91		
IV: 11 EC	F	1945	N									1											3/66	8	12	139		
IV: 19 LOA	M	1950	N																				11/62	2 1	13	75		
IV: 20 KA	M	1948	N																			–	10/62	2 2	12	114		
IV: 22 AKL	F	1950	N																			–	2/63	3 4	10	120		
IV: 23 BS	M	1954	N																				11/62	1 3	12	63		
IV: 32 BH	F	1943	N																				11/62	2 2	11	67		
IV: 35 RN	F	1950	N																				10/62	2 2	19	82		
IV: 36 AN	F	1952	N																				10/62	3 1	18	71		
IV: 40 BP	M	1947	N																				10/62	2 3	13	81		
IV: 41 GP	M	1950	N																				10/62	2 2	12	73		
IV: 48 IK	F	1950	N																				11/62	1 1	11	104		
IV: 51 IA	F	1958	N																		W n1	–	11/62	3				

Table 2 (Continued)

Family 42 (continued)

Case	Sex	Born	Type	Bleeding history N	O	TS	TO	T	E	GI	UT	M	Part	O	FII	P	Tr	J	Misc	TE	Op	Sum	Examination Date m/year	D ke min.	Ivy min.	AIIF	Sz	Remark
																							5/62	>30 10	30	30		
																							8/67		30	45	1	
III 26 EN	F	1940	M	2								1	0		1		1			1		+	5/62	9 9	>30	43		
																							1/67	2 5	30	30	16	
																							9/67	6 >30	>30	32	18	
III 27 KZ	F	1930	M	1	1								3		1		1			1		+ +	10/62	3 3	>30	42		
																							8/67		30	40	12	
III 28 KE	F	1939	MI	1																1	Gyn/ Salp/ + app/	+	10/62	2 3	30	79		
III 31 IS	F	1932	M	1	1								2							1		+	11/62	4 3	4	44		
III 32 NOA	M	1934	MI	2												1				2	App	+	11/62	5 4	>30	41		
																							8/67		>30	40	10	
III 33 BAA	M	1937	MI	2	1										1				Eye 2/	2	App	+ +	12/61	3 2	4	38		
																							1/62	4 2	79	30		
																							8/67		21	45	1	
III 35 KS	F	1940	MI	1								3			1		1			2		+ +	10/61	15 6		43		mem VI
																							5/62	1 8	>30	35		
																							8/67		>30	45	1	
																							10/68			35	7	
I 37 IBK	F	1934	MI		1								2									+	5/62	4 3	30	36		
																							8/67		21	40	6	
I 39 JIA	M	1946	MI																			–	11/62	3 2	>30	44		
																							8/67		16	45	6	
I 40 LA	F	1948	MI	1	1							1	0							1	Veg ad 2	+	5/62	3 1	77	41		
																							8/67		2		0	
I 42 MP	F	1953	MI									1	0			1					To	–	11/62	2 3	>30	55		
																							8/67		10	70	39	
7 JFF	M	1949	MI	2	1		1								1					1		+	5/62	2 8	25	48		
																							8/67		9	43	31	
12 IC	F	1948	MI	1	1	2						2	0		1	1	1			2		+ +	1/63	>30	>30	34		
16 TÅ	M	1951	MI	1																		–	10/62	2 3	>30	53		
17 LÅ	F	1952	MI																			–	10/62	1 2	>30	37		
18 ChÅ	F	1956	MI												1					1-		–	10/62	3 3	>30	31		
24 BB	F	1958	MI																	2		+	11/62	3 3		38		
31 HIH	M	1940	MI																	0		–	11/62	3 3	1	43		
33 LH	M	1945	MI														1			1		+	5/62	3 3	25	54		
34 OH	M	1947	MI		1															1		–	11/62	3 3	25	43		
39 JN	M	1959	MI	2	2										1		2			1			3/63	>30		49		
																							8/67		>30	40	0	
VI 44 MZ	M	1958	MI	1																		+	10/62	4	>30	70		
																							8/67		28	40	9	
VI 45 AZ	F	1961	MI												1		1			0		+	8/67		>30	38		
IV 46 ME	M	1958	MI												1		2/			0		+	10/62	4	>15	79		

Table 2 (continued) *Family 48*

Case	Sex	Born	Type	N	O	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
																								Bleeding history / **Examinations**				
III 1 BH	F	1960	S	1			1	1			1				1		3r	2r		1		+ +	1/64	> 30		11		
																							1/63	> 30				
																							5/67		> 30	20		
																						–	5/67	1 1	14	65		
II 1 KH	M	1930	N																				11/67	1 4	15	90		pregnant
II 2 MO	F	1939	N																				11/68	1 2	11	140		

Family 49

Case	Sex	Born	Type	N	O	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	T	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III 3 AO	F	1919	MI	1								3					2		Jcr 17	1	App	+ +	3/61	2 4		57		
																					Salp 2							
																					Curett		9/61			66		
																					Mam		6/65	4 5	11	50		
																							11/66	4 6	21	69		
I 2 EN	F	1842	(M)	1								1																
II 1 KA	F	1873	(M)	1								1																
II 3 AA	M	1879	(M)	1						2	2						1		Icr 13*	1								fatal
III 1 AE	F	1910	MI	2	2							1					1			1	Mam 2	+	3/61	2 1		70		
																					Curett 1		9/61			5		
																					Gyn		6/65	2 2		63		
																							11/66	2 2		5		
IV 3 GS	F	1945	M										3									+	11/66	2 3	8	58		
																							12/67	1 3	11			
III 2 HA	M	1913	N																				11/66	1 2	7	78	72	
IV 2 HE	M	1940	N																			–	6/65	3 2		75	38	
IV 7 JB	M	1943	N																				11/66	2 3			54	

Family 50

Case	Sex	Born	Type	N	O	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sum.	Date m/year	Duk min.	Ivy min.	AHF %	Sz %	Remarks
III 1 IA	F	1955	MI	1									0							2	App 2	+	/65			3.		
																							12/67	1	> 30	60	11	
I 2 MA	F	1927	MI	2	1					3r		3	3322		1		1			2r	App 1	+ + +	/65			55		
																							12/67	7 7	30	55	0	
II 2 GA	F	1958	MI	1	1			2							1		1			0		–	/65			2		
																							12/67	4	> 30	70	0	
II 3 EA	M	1959	MI		1										1		1			0		–	12/67	7	30	75	34	
II 4 GA	F	196.	(MI)	1											1													

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF	Sz	Remarks
										Bleeding history														Examinations				
III 3 SÅN	M	1946	M	3		1			2						1		1			2	Veg ad		12/51	>1'0*				test at local hosp.
																							12/51	9*				
																							2/52	> 60*				
																							4/52	5				
																							5/61	1 >'0		53		
																							8/61	>60		49		
																								>60				
II 2 MN	F	1914	M								2	1			1								10/61	11 11		73		
																				1	Chol Curett		1/67	4 2	30	43	0	
																							1/67	11 14*	19	80	5	had taken acetylsalicylic acid
III 1 MN	F	1942	I I	2																								
III 2 HEN	M	1944	N										0							1			1/67	2 4	12	75	18	
																				1		–	1 67	3 3	10	65	69	

Family 53

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
										Bleeding history														Examinations				
III 2 IW	F	1929	MI	1								2	22(3)							2	Sect caes 3 Curett		12,6..	3 3	15	88		
																							5 63	6 7	12	58		
																							6 63	4 3	~30	42		
II 3 RÅ	F	1903	(M)									1											12/66	4 4		44	26	
III 1 SÅ	M	1926	MI						3	2					2					2			11/68			54	14	
III 3 EJ	F	1939	N														1			1	Gastr App		7'63	3 3	13	57		
IV 1 KW	M	1950	N												1								7'63	4 3	15	60		
IV 2 AW	F	1953	N																			–	12/66	2 5	13	119	79	
IV 3 MW	M	1962	N																			–	7/63	4 3	18	131		
																	1					–	6/63	5 5	14	97		
																						–	11/63	7		137		
																							11/68		13	112		

Table 2 (continued) *Family* [illegible]

Table 2 (continued) *Family 34*

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	T	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III 2 PD	F	1954	M									2/	0							2	Veg ad 3*	++	5/63	5	22	34		Platelets postop. 38,000/mm³
																							1/67	5 18	27	40	3	
I 3 LP	M	1889	(M?)	1																								
II 4 HF	M	1912	(M)	1																								
II 7 MD	F	1920	MI	1							1	1	1								App	+	5/63	2	8s	65		
																							9/64		3	107		
																							11/64		23s	110		
																							1/67	2 5	18	46	0	
II 10 VP	F	1929	(M)	1											1													
II 11 BP	M	1932	(MI)	1																								
II 3 ND	M	1920	N																			–	1/67	1 1	11	45	8	
																							11/67	2 0	15	90	11	
III 1 BD	M	1948	N																			–	1/67	2 2	15	85	9	

Family 35

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
IIIb 3 GF	M	1948	M				3								1								4/62	3		49		
																							7/63	3	30	35		
																							8/63		39			
I 3 AK	M	1908	(M)	1						3										2	Gastr 3*							
II 8 LF	F	1933	fat.																			–	7/63	3	12	107		f tal
																							8/63	2 1	9	5		pregnant
																							10/69		9	49		pregnant
II 5 RF	M	1925	N																			–	8/33	2 3	11	107		
III 1 LF	M	1953	N																			–	7/63	2	18	107		
III 2 AF	F	1955	N																			–	7/63	3	18	79		

Family 36

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
IIb 2 OW	M	1902	MI	2	2										1		1		Hae-morrh 2	1			10/63	6 6	>30	5		
																							10/63	4 >30	>30	70		
																							11/63			25		

Table 2 (continued)

Family 58

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	T	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz	Remarks
								Bleeding history																Examinations				
III 9 AF	M	1937	M	1				2							1		1			3		+	5 63	30				
																				1			9'63	7 4	30	35		
																							9'63	~30 9	6	7		
																							5'67				0	
II 1 FA	F	1892	(M)	1																								
II 2 KF	M	1905	Mi	2					1								2			1			5'67	2 7	~30	45	11	
II 3 EF	M	1909	(M)	1																								
III 1 AMO	F	1937	Mi	1				2					3 2							1	To 2	+	1 /67	3 3		40	17	
III 3 POF	M	1941	Mi	2																2		+	12 67	4 2	~30	40	49	
III 5 KEF	M	1948	M	1							1												5'67	1 2	7	50	3	
III 6 IF	M	1951	M	1													1	1					10 63	6 6	~30	49		
																							5'67				8	
III 8 IF	F	1954	M	2	1								0		1								10 63	7 4	~30	60		
																							5'67				8	
II 4 QF	F	1919	I ι									1	1111										9 63	3 4	70	116		
																							5 67				14	
III 4 TW	F	1946	N																				1_/67	1 1	11	85	57	
III 7 GF	F	1952	N																			−	5 67	1 1	1	90		

Family 59

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
								Bleeding history																Examinations				
III 1 TA	M	1944	M																	0	To 3	+ +	10 63	5 3	14	6_		
																							10'63	10 18	>30	43		
I 1 FN	M	1892	(Mi)														1											
II 2 SA	F	1900	Mi	2								2					1		Mis-carr 1	2	Veg ad I		5 67	4 4	18	68	19	
II 5 KN	F	1923	Mi									2			1		1			2		+	5,67	6 1	23	63	0	
II 7 GO	F	1933	Mi												1		1			2		+	5'67	3 2	14	50	7	
III 4 IA	F	1957	Mi	1			1													1		−	5/67	3 1	--	50		
III 9 EN	F	1959	M	1	1										1		1			2		+	5'67	1 1	9	50		
II 4 RB	F	1922	Int												1		1			2		+	5/67		18	120	17	
III 1 GA	M	1918	N	1																			12/67	1 1	13	140		
III 3 IWA	F	1955	N																			−	11/67	4 3	6	65	77	
III 5 KB	M	1944	N	1																		−	5/67	1 0	8	105		
																						−	9/68	3 1	9	117		

Table 2 (continued)

Family 60

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part	O	EH	P	T	J	Misc.	TB	Op	Sum	Date m/year	Duke min.	Ivy min.	AHF %	Sx %	Remarks
																												Bleeding history / Examinations
III:2 LJ	M	1956	M				2								1		1			2		+	9/63	15*		37		test i local hosp.
																				6			11/63	>30	~30	35		
																								>30				
																							12/63	>30		35		
II:10 ES	F	1929	M	2	1							3			1	1	1			1	Hy 3	+ +	5/67	4 5	>30	48*	0	
																					Ict 2							
																					Curett	+ +	11/63	5 5	>30	35		
II:13 IJ	F	1933	Mi	2								3			1						T	–	6/64	6 5	>30	113		
III:1 MJ	F	1953	Int										0										6/64	5 5	>30	65		
																	1					–	5/67	1 2	6	50*	13	
II 3 LS	M	1950	Int.																			–	6/64	1 1	12	120		
I:4 HJ	M	1929	N																									

Family 61

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TB	Op	Sum.	Date m/year	Duke min	Ivy min.	AHF %	Sx %	Remarks
																												Bleeding history / Examinations
I:1 ALK	F	1937	M	2								3								2	T 2		1/63	5 4		48		
																					Hy 3		2/63	4	2.	39		
																					Curett 1		10/63			39		
																							1/67	2 3	10		0	
II:1 EK	F	1938	Mi	2i				2							1					6		+	3/63	6		35		
II:2 KP	M	1940	Int	2																			1/67	1 2	14	90	16	
II:2 MJ	F	1914	N																				1/67	1 1	9		28	
II:3 BP	M	1944	N																			–	1/67	1 1	10	75	56	

… 2 (continued)

Family 63

Case	Sex	Born	Type	N	O	TS	TO	T	E	GI	UT	M	Part	O	EH	P	Tr	J	Misc.	TE	Op	Sem	Date m/year	Duke min	Ivy min	AHF %	Sz	Remarks
II 5 GL	M	1880	M	1						3					2	1	1		IIpt I Im 2/									
II 1 HL	F	1871	(Mi)	1																			7 65	1				
II 6 JL	M	1884	(Mi)																				7/65	17				
III 4 GL	M	1923	M																				7'65	2				
IV 1 ACL	F	1942	Int							3													7'65	2				
																							6,67			9		
IV 2 ML	F	1943	Int									0								2-					30		0	
III 1 NL	F	1907	N									0											11'67	3 6	30 55			f tal
III 2 OL	M	1911	N																				5'67	1 1	11 55	70		
III 3 EL	M	1918	N																1				6/68	2 3	9 45*			
IV 3 LL	M	1951	N																				5/67	1 4	14 40*			T kes p- pills
IV 4 KL	M	1953	N	1																			6/68	1	7 35	76		Takes p- pills
																							6,67	4 4	15 60	72		taken salicyl
																							9 67	2 3	11 70	33		
																							6'67	2 4	8 55	64		
																							6 67	2 2	12 55	31		
																							11'67	3	13 80	19		
																							11/67	2 2	11 80	6		

Family 64

Case	Sex	Born	Type	N	O	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sem.	Date m/year	Duke min.	Ivy min.	AHF %	Sz /	Remarks
I GJ	F	1950	M	1						3			0		2		1		Tooth- 0 erupt I			+ +	4/63			40		
GK	M	1896	(Im.)	1																								
MJ	F	1911	N									1					1						9'63	30	39s	65		
																	1		Chol				6/67	12 2	-30	35		

Table 2 (continued)

Family 65

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
IIh 1 BS	F	1922	M	2	1				1			3	0		1		1		Mis-carr 1	1	Chol	+ +	10/57	34 24		111		upper resp. infect
																			Coit 1		App		1/64	9 5	11 s	78		
																					Mam		2/64			39		
																					Curett 1		4/64			32		
																							1/67		> 30	29	17	
I 1 PGÅ	M	1866	(M)	1											1		2			2	App	+	5/67	6 6	> 30	57	2	
II 2 LA	F	1895	Mi									1	0		1		1				Hy	+	1/67		> 30	30	5	
II 3 LR	F	1897	MI	1	1																Mam							
II 6 EMÅ	M	1906	(MI)	1								2	3								To	+ +	1/67	2 4	25	45	2	
IL 7 AL	F	1911	Mi	1																	App	+	1/67		> 30	43	10	
III. 5 LL	M	1942	MI	2																		–	5/67	1 1	6	59		
III: 2 SR	F	1929	N																									

Family 67

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III: 1 AÅ	F	1949	MI	2								1	0							2	T 3	+ +	10/64	4 6	18	52		
																							8/65	7 4	76	55		
																							5/67	2	9	37		
																							8/65	5 4	30	105		alcoholic disease
L 1 RÅ	M	1923	MI	1						3							1			1	App Vertebr 3	+ +	9/65	4 4	23	87		
																							10/65	2 2	30	52		
																						–	10/64	2 2	11	54		
L 2 EÅ	F	1924	N																				8/65	3 3	14	100		
																							8/65	2 2	16	97		
II: 2 CÅ	M	1957	N																									

Table 2 (continued)

Family 70

Case	Sex	Born	Type	Bleeding history: N	G	TS	TO	T	E	GI	UT	M	Part	O	EH	P	Tr	J	Misc.	TE	Op.	Sam.	Examinations: Date m/year	Duke min.	Ivy min.	AHF	Sz	Remarks
II.1 KH	F	1938	M	1											1						Chol 3		10/64	1**				Test 1 local hosp
																					Mam 3		11/64	1	8s	59		
																							11/64	2	13s	6		
																							11/64		40s			
																							11/67	4 4	19	45	65	
III.2 TH	M	1959	M	2																	Hernia		1/67		11	50	17	
I.2 LM	F	1913	(Int.)									1																

Family 7

Case	Sex	Born	Type	Bleeding history: N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sam.	Examinations: Date m/year	Duke min.	Ivy min.	AHF %	Sz	Remarks
III.1 BB	M	1959	M	2											1	1				0	Veg ad		9/64	3	18s	37		
																							5/67		30	53	10	
II CB	F	19?7	Int							1			1								Gyn	+	9/64	1		51		
																							10/64		9s	78		
																							5/67		18	5	21	

Family 73

Case	Sex	Born	Type	Bleeding history: N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sam.	Examinations: Date m/year	Duke min.	Ivy min.	AHF	Sz	Remarks
II.5 BE	F	19?5	Mi		1							3								2	T 1		8/64			43		
																					Hy 3		9/64		13s	21		
																					Ov		6/67	3	2s	43		
I.2 EJ	F	1896	(M)	1							2	3							Mis-carr 3		Hy							
																					Thyr 3*							
II.3 SJ	M	1923	MI	2															Eye 2	2	Nose 2	+	6/67	1 2	17	35		f tal(?)
III.2 POE	M	1957	MI	1																1		+	6/67	4	>30	33		
																				1			6/67	3	30	33		
II.1 SJ	M	1919	Int.	1											1		2			2		+	6/67	1 1	11	75		
II.2 SQ	F	1921	N																			–	6/67	1 1	6	170*		
II.4 BE	M	1919	N																			–	6/67	3	9	117		
III.1 CGE	M	1952	N																			–	6/67	3	4	138		

Table (continued)

Family 74

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part	O	EH	P	T	J	Misc.	TE	Op.	Sum	Date m/year	Duk min.	Ivy min.	AHF %	Sz %	Remarks
II: 1 EB	F	1909	M									1		2	1		1			2	Ov Gyn		9/64	4	13s	67		Menopaus
																							10/64		12	23		
																							12/64		16	37		
																							10/68	9 3	12		37	

Family 75

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part	O	EH	P	Tr	J	Misc.	TE	Op	Sum.	Date m/year	Duke min.	Ivy min	AHF %	Sz %	Remarks
II: 1 BT	M	1928	M		1										1		1			3	Herniar Vertebr 2 Mastoi	+	1/64	7 5	16	43		
																							12/64	4 4	16	5		
																							11/66	2 2		45	0	
I 2 MT	F	1906	MI																				11/66	2 3	16	35		
																							5/67			37	42	
I. 1 GT	M	1905	N																				11/66	1	13	81	0	
II 2 IT	M	1931	N																				11/66	1 0	13	59	79	
III 1 MT	M	1952	N																				11 66	2 2	10	87	35	
III 2 LT	M	1955	N																				11 66	1 2	8	1_8	50	
III 3 LT	F	1958	N																				11 64	3 3	13	73		

Family 76

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc	TE	Op	Sum	Date m/year	Duke min	Ivy min	AHF	Sz	Remarks
III: 2 FB	F	1900	MI		1					3		1	0		1		1			2	Hy 2		1 63	9 10		_3		
																							2 63	7	13	7		
																							5 67	7 4	19	90	_5	f tal
		1859	(MI)							3*											Ves stone 3		1 67	2 1	11	90	1	
		1892	N																									

 Table 2 (continued)

Family 77

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
													Bleeding history										Examinations					
Ib 7 HR	F	1941	M	1								3	+		1		1			+	Appt	+ +	6/63	35				test at local hosp. mens VII
																					Caretl		12/64	16 15		97		
																					Thyr		11/65	16 15	>30	40		
																							11/66	8 30	>30	44	0	
																							5/67			49		
I 3 GJ	F	1906	M	1									1				1				Ear	+	12/66	1 3	15	63	17	Menopaus
II 6 GJ	F	1939	M		1			1			1		0									+	11/66	2 2	14	47	32	
I 2 BJ	M	1890	N							2									Hae-morrh 1			+	12/66	1 1	6	83	55	
II 1 ME	F	1970	N									1									T App	–	12/66	1 2	8		0	
II 2 BS	F	1923	N																				6/67	1 1	13	50		
II 3 KJ	M	1927	N																			–	1/67	2 2	10	145	–	
II 4 DJ	M	1937	N																			–	12/66	3 3	14	59	6	
II 5 RJ	M	1938	N																				12/66	1 1	10	44	38	
																							7/68	2 3	12	70	45	

Family 78

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz	Remarks
													Bleeding history										Examinations					
Ib 1 HA	M	1957	M1												1		1			2		+	12/64	3 4	32	7		
																							1/65	3 4	.2	18		
																							1/65			17		
I 1 TA	M	1918	Int.	2																1			1/65	4 4	13	107		
																							2/65	5 5	13	114		
I 2 VA	F	1932	N																			–	1/65	2 2	14	139		

Table 2 (continued)

Family 81

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TB	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
												Bleeding history												Examinations				
II 3 NF	F	1902	M									1			1					1	Chol	+	2/65	3 4	38	54		Menopaus
																					Appr							
																					Curett		2/65	3 5	24	87		Menopaus
																					Eye 2		11/66	2 3	2	77		Menopaus
II 6 VS	F	1910	Mi		1							2			1				Haemorrh 1	1	Curett	+	11/66	2 1	21	103	0	Menopaus
II 7 ES	F	1913	M		1							1	0		1						Chol 3	+	11/66	4 9	>30	67	3	Menopaus
II 11 BC	F	1923	Mi										2		1		1			2		+	11/66	1 2	25	50	74	Menopaus
II 10 AL	M	1921	Int														1			2		+	11/66	3 1	16	103	19	
II 4 AN	F	1904	N																			–	11/66	1 2	19	108	24	
II 8 KL	M	1915	N																			–	11/66	1 1	14	74	42	
II 9 EL	M	1918	N																				11/66	1 2	14	65		
III 2 GF	M	1928	N		1										1								11/66	1 2	9	103	65	
III 3 RF	M	1936	N																				11/66	1 2	12	60	36	
IV 1 RM	M	1950	N																			–	11/66	2 2	16	65	7	

Family 82

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part	O	EH	P	Tr	J	Misc.	TB	Op	Sum	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
												Bleeding history												Examinations				
II 1 AT	M	1955	MI								2								Dent. absc 2	+		+	4/65	3 3	21	37		
																							4/65	3 3	22	49		
I 2 UT	F	1923	Int.																			–	4/65	3 3	26	63		
																							4/65	3 4	23	60		
																							5/65	3 4	4	80		

58 *Table 2* (continued)

Family 77

Case	Sex	Born	Type	N	O	TS	TO	T	E	GI	UT	M	Part	O	EH	P	Tr	J	Misc.	TE	Op.	Sam.	Date m/year	Duke min.	Ivy min.	AHF	Sz	Remarks
			Bleeding history																				Examinations					
IIb 7 HR	F	1941	M	1								3	1		1		1			r	App/	+ +	6/63	35				test t lo- c l bosp mens VII
																					Curett		12/64	16 15		97		
																					Thyr		11/65	16 15	>30	40		
																							11/66	8 30	30	44	0	
																							5/67			49		
I 3 OJ	F	1906	Mi	1									1				1				Ear	+	12/66	1 3	15	63	17	Menopaus
II 6 OJ	F	1939	M		1			1			1		0									+	11/66	2 2	14	47	32	
I 2 BJ	M	1890	N							2									Hae-morrh I			+	12/66	1 1	6	83	55	
II 1 ME	F	1970	N									1									To App		12/66	1	8		0	
II 2 BS	F	1923	N																				6/67	1 1	13	50		
II 3 KJ	M	1927	N																				1/67	2 2	10	145	2	
II 4 DJ	M	1937	N																				12/66	3 3	14	59	6	
II 5 RJ	M	1938	N																				12/66	1 1	10	44	38	
																							7/68	2 3	12	70	45	

Family 78

Case	Sex	Born	Type	N	O	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sam.	Date m/year	Duke min.	Ivy min.	AHF	Sz	Remarks
			Bleeding history																				Examinations					
II 1 HA	M	1957	M												1		1			2		+	12/64	3 4	3	7		
																							1/65	3 4	2	18		
																							1/65			17		
I 1 TA	M	1918	Int.	2																1			1/65	4 4	13	107		
																							2/65	5 5	13	114		
I 2 VA	F	1932	N																			–	1/65	2 2	14	139		

Table 2 (continued) Family 90

Case	Sex	Born	Type	N	O	TS	TO	T	E	GI	UT	M	Part	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remark
IIh 1 ML	M	1965	Sv	3r	1		2								2		2			0		+ + +	11/65	>60*				test at local hosp.
																							11/65					
																							12/65		>45	3		
																							10/66	26				
2 IJ	F	1905	(Int)		1										1				1 m. 1			+	1/66	6	12s	55		
3 IBL	F	1942	M		1							1			1								10/66		12s	53		
																							1/66		4s	107		
1 UL	M	1943	N		1												1						3/66	3	3	44		
2 BJ	M	1935	N		1																		9/66		5s	71		
																							4/67			82		

Family 91

No	Sex	Born	Type	N	O	TS	TO	T	E	GI	UT	M	Part	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
1 MS	F	1945	M	1				1				1	0		1		1		IIpt 1	2	Veg ad 2	+	1/66	2 2	15	73		
																				/	T 2		1/66	2 2	21	68		
																							2/66	2 1	17	54		
																							2/66	2 10	4	43		
																							11/67			53		
1 RS	M	1917	(M)							2											Gastr 3*							f tal
3 LS	M	1950	Int	2																			6/66	1 2	11	87		
																							6/66		12	48		
																							6/66		15	90		
2 OS	F	19_2	N																				6/66	2 1	10	196		
2 LS	F	1947	N																				6/66	5 2	14	119		

Family 92

No	Sex	Born	Type	N	O	TS	TO	T	E	GI	UT	M	Part	O	EH	P	T	J	Misc	TE	Op.	Sum.	Date m/year	Duke min	Ivy min	AHF	Sz	Remarks
3 1 AM	F	1965	S	3r											1		2		kr 1? Retro-per 1 /	0			4 66	10		11		
																							12/69	~30				
2 OS	F	1918	(M)	1											1													
2 OM	F	1937	M	2											1							+	5/68	7 8	10	53	7	T kes p-pills
3 DS	F	1943	(Int)												1													
1 MM	M	1939	N																				5/68	3	15	50	24	

Table 2 (continued) *Family 86*

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part	O	EH	P	T	J	Misc.	TE	Op	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sx	Remarks
													Bleeding history												Examinations			
III 1 AMÅ	F	1929	M	1	1					3		1	1 1		1				Miscarr 2		Chol 2	+ +	5/64		16	57		
																							9/64		11 s	60		
																							12/64		6 s	63		
																							1/67	4 5	21		5	
IV 2 CÅ	F	1960	M												1		1					+	1/67	1 3	23	60	0	
I 2 SO	F	1881	(I t)												1													
II 3 SO	F	1910	(Im)												1				Miscarr 2									
II 1 HK	M	1898	N																			–	1/67	1 1	14		7	
IV 1 ACÅ	F	1950	N																			–	1/67	1 1	18	55	1	
																							8/68		8 s	95	31	
IV 3 MÅ	F	1964	N																			–	1/67	2	11	85		

Family 88

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sx	Remarks
													Bleeding history												Examinations			
II 2 HI	F	1916	Mi										0							1	Hy 3t	+ +	5/65	4 5		47		
																							6/65	3 3	10	37		
																							6/65	3 4	>30	4		
																							11/66	1 2	13	28	6	
I 2 BH	F	1887	Im																			–	11/66	2 2	2	10*	0	Menopaus
II 1 SE	F	1907	N																			–	11/66	1 2	7	88	31	
II 3 GB	F	1920	N																			–	6/66	3 3	11	110		
II 4 HI	F	1922	N																			–	6/66	2 2	8	100		

Family 89

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sx %	Remarks
													Bleeding history												Examinations			
IIIb 2 BN	M	1922	MI	1	1					3					1		1					+ +	9/65	6	16 s	28		
																							2/66		14 s	50		
																							1/67	4 1	>30	50	25	
I 1 NW	M	1900	(M)	1																								
II 2 HN	F	1887	MI	2	1					3t		2			1		1			1	Fract 2	+ +	1/67	1 2	25	45	6	
IV 1 MN	F	1951	MI									1	0								T	–	5/67	2 1	30	48	16	
IV 2 ON	F	1954	Int.																			–	5/67	1 1	79	95		
III 1 KN	M	1920	N																		T	–	11/67	2 3	10	75	8	

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	T	J	Misc.	TE	Op.	Sam.	Date m/year	Duke min.	Ivy min.	AHF %	Sx %	Remarks
IIb 1 ML	M	1965	S	3/	1	2									2		2			0		+ + +	11/65	60*				test 1 local hosp
																							11/65					
I 2 IJ	F	1905	(Int)	1																			12/65		>45	3		
II 3 IBL	F	1942	M	1											1								10/66	26				
												1			1				1 m. 1									
II 1 UL	M	1945	N	1																		+	1/66	6	12	55		
II 2 BJ	M	1935	N	1													1						10/66		12x	53		
																						+	1/66		4x	107		
																						–	3/66	3	3	44		
Family 91																							9/66		5	71		
																							4/67			82		

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part	O	EH	P	Tr	J	Misc.	TE	Op	Sam.	Date m/year	Duke min.	Ivy min.	AHF %	Sx	Remarks
IIb 1 MS	F	1945	M	1				1				1	0		1		1		Hpt 1	2	Veg ad 2	+ +	1/66	2 2	15	73		
																				t-	T 2		1/66	2 2	21	68		
I. 1 RS	M	1917	(M)																				2/66	2 1	17	54		
II. 3 LS	M	1950	Int	2						2													2/66	2 10	4	43		
																					Gastr 3		11/67			51		
I 2 OS	F	1922	N																			+	6/66	1 2	11	87		fatal
II 1 S	F	1947	N																				6/66		12	48		
Family																							6/66		15	90		
																						–	6/66	2 1	10	196		
																						–	6/66	5 2	14	119		

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	T	J	Misc.	TE	Op.	Sam.	Date m/year	Duke min.	Ivy min.	AHF	Sx	Remarks
IIb 1 AM	[illegible]	1965	[illegible]	3/																								
[illegible]	[illegible]	1918	(M)	1										1			2		Ier 1 ?	0								
[illegible]	[illegible]	1917	M	2															Retro-				4/66	10	11			
																			per 1 ?				12/69	30				
[illegible]	[illegible]	1941	(Int)											1														
		[illegible]	N											1														
														1									5/68	7 8	16	55	7	T hes p-pills
																							5/68	1 2	15	50	24	

 Table 2 (continued)

Family 93

Case	Sex	Born	Type	Bleeding history: N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum	Examinations: Date m/year	Duke min.	Ivy min.	AHF %	Sz	Remarks
II 2 LB	M	1937	M		1															2	Dent. bac 2	+	4/66	16 3	16	3		
																							4/66	6	16	3		
																							5/66	4 4	30	28		
II 1 BB	M	1934	Int																			–	12/67	5 6	10	55		
I 1 EB	M	1910	N																			–	11/68	2 3	9	80	32	
I 2 MB	F	1913	N																			–	11/68	1 2	8	88	54	

Family 100

Case	Sex	Born	Type	Bleeding history: N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Examinations: Date m/year	Duke min	Ivy min	AHF %	Sz %	Remarks
III 4 AS	M	1963	Mi				2										1	1	1	12		++	7/66	3 3	30	25		
																				1			7/66	5 5	7	1		
																							8/66		19	34		
																							11/68				20	
I 1 GL	M	1900	(Mi)							3	1				1		1			2								Fatal
II 2 MS	F	1928	MI									1							Mis-carr 1			–	7/66	3 3	16	35		
																							7/66	2 2	19	35		
																							8/66	1 1	13	4		
III 6 JN	M	1966	Mi				1								2		2	2	1	0		++	12/67	>15		20		
																							12/67	5 6	>30	17		
II 4 CN	F	1943	Int.																			–	12/67		10	50		Takes p-pills
II 1 AS	M	1921	N																			–	8/66	2	8	50		
																							9/66	1 1	14	80		
III 1 PS	M	1955	N																			–	7/66	3 3	12	68		
																							9/66	2 2	14	110		
III 2 KS	M	1950	N																			–	8/66	4 4	14	117		
III 3 JS	M	1953	N																			–	8/66	2 3	17	101		
III 5 MN	F	1963	N																			–	12/66	3 3		78		

Table 2 (continued)

Family 101

				Bleeding history																				Examinations				
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	T	J	Misc	TE	Op.	Scan.	Date m/year	Duk ml	Ivy min	AHF %	Sx %	Remarks
Ib 1 MO	F	1927	M	2								3	113		1						Chol r	+ +	6/66	3	4	25		
																					Joint		6/66	4	30	40		
																					App	+	11/67	3 1	14	56		
I 1 HT	M	1899	M	2	1																	+	9/66	2	13	55		
II 2 BJ	F	1928	Mi		1							1			1	1						–	11/67	3 7	>30	30		
II 3 AMF	F	1933	M												1					2		+	11/67	1	30	45	0	
III 5 AF	M	1957	Mi							1													6/66		10	49		
III 2 KO	F	1959	Int																			–	11/67	2 2	14	90		
I 2 OT	F	1900	N	1																			6/66		5	74		
III 1 AO	M	1955	N	1																			9/66			84		
III. 3 AJ	F	1957	N																				9/66			99		
III 4 MJ	F	1959	N																									

Family 103

				Bleeding history																				Examinations				
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	T	J	Misc	TE	Op.	Scan	Date m/year	Duke min	Ivy min	AHF %	Sx %	Remarks
Ib 3 AW	F	1959	Sv	2	3	3	2r								1		2		Umbil 1	3		+ + +	1/62			20		
																			Eye 1	r-			11/63			5		
																							1/64	>13				
																							10/66	>25	>30	32	0	
																							10/66	>25		25	10	
I 1 WW	M	1924	M	2																	Gastr r	+	10/66		13	63	24	
																							10/66	2 3	19	70	4	
I 2 MBW	F	1930	Int																			–	10/66	2 5	16	90	58	
																							10/66	3 4	22	88	67	
II 2 JW	M	1956	Int																			–	10/66	4 4	28	91	30	
																							5/67	2 2	19	129	37	
II 1 JW	M	1951	N																			–	10/66		12	68	3	
																							10/66	3 3	12	69	0	

56 *Table 2* (continued)

F mily 105

Case	Sex	Born	Type	N	O	TS	TO	T	E	GI	UT	M	Part	O	EH	P	Tr	J	Misc	TE	Op.	Sum	Date m/year	Duke min	Ivy min	AHF	Sz	Remarks
										Bleeding history														Examin tions				
III 1 IN	F	1924	M	2	1							3			1	1			Cot 2		T		11/67		30	76	15	
																					App		11 67	9 5	4	49	4	
																							2/68	3 3	30	59	4	
I ALE	F	1873	(Mi)							3																		
II 2 GJ	F	1901	M	1											1							–	10,68	3 5	70	63*	40	Menopause
II 3 TJ	F	1907	M	1	1								0							2	App		10 68	1 1	17	45*	46	
II 1 AJ	M	1892	N								1												10/68	1 1	15	174	79	

Family 107

Case	Sex	Born	Type	N	O	TS	TO	T	E	GI	UT	M	Part	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF	Sz	Remarks
										Bleeding history														Examinations				
II 2 MB	F	1935	Mi	2	1							1			1						Chol 3	+ +	9 66	7 5	~20	45		
																							9 66		>30	43		
																							10,66			82		
																							3/67	3 2	30	45	0	
II 3 MM	F	1944	I t																			–	11/68	3 1	30	213	70	
III 1 CB	F	1958	Int												1							–	10 66	2 2	~30	77		
																							3/67	1 3	,5	107		
II 1 MBÅ	F	1931	N										1									–	9/67	4 4	11	88		
III 2 IB	M	1960	N																			–	10,66	6 8	18	77		
																							3/67	1 1	13	70		
III 3 MB	F	1964	N																			–	10/66	3	13	96		

Family 109

Case	Sex	Born	Type	N	O	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sum	Date m/year	Duke min.	Ivy min.	AHF	Sz	Remarks
										Bleeding history														Examinations				
III 2 LA	M	1926	MI	1	1												1			2		+	5/67	1 70	28	79		
																							10 67	4 9	16	39	5	
																							12/67		>,5	43		
I 1 JA	M	1897	MI																		Prost 3		12/67	1 1	14	35		
III 1 AA	M	1952	M	1	1																		12/67	1 1	10	48	0	
III 2 KA	F	1952	N																				12/67	2 1	10	118	44	

Table (continued)

Family III

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part	O	EH	P	Tr	J	Muc.	TE	Op.	Sum	Date m/year	Dok min.	Ivy min.	AHF	Sz	Remark
																					Bleeding history				*Examinations*			
																				31		+ +	12/67	4	[illegible]	34		
II: 2 TE	M	1962	M												1					f-			12/67		20	32		
																							12/67		7	30		
																							1/68		30	70	40	
																					App	+	1/68	2	>30	44	9	
L 2 ABB	F	1938	M	2																			1/68		18			
																							1/68	3	1	35		
II 3 AE	F	1963	M																				1/68	4	10	47		
II 1 KE	F	1959	Int																				1 68			39		
																							1/68		8	1 4		
I 1 PE	M	1936	N																									

Family B

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part	O	EH	P	T	J	Muc	TE	Op	Sum	Date m/year	Duke min.	Ivy min.	AHF	Sz	Remark
																					Bleeding history				*Examinations*			
II 1 AB	F	1942	M							2		1	1		1						To		12/67	3 2	19	90		
I 1 OB	M	1912	I t	1																			12/67	1 1	16	68	37	
III 1 AMB	F	1961	N																				12/67		10			

Intracranial bleeding — EEG during adolescence showed changes, possibly due to bleeding after fall from horse.

The patient *died* at 24 years in Greece from intracranial bleeding after trauma against left temple (slap with flat hand). No fracture. Post mortem examination revealed a large haematoma compressing left temporal lobe.

Post-extraction haemorrhage — At 10–11 years dental treatment at two sittings. Bleeding required 6 and 5 bottles of blood.

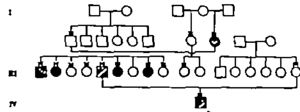
At 17 years dental treatment under protection of F I-O 500 ml before and 600 ml within 5 days after op. Three days after last infusion she had profuse gingival bleeding with fall of Hb to 5.1 g/100 ml. Received 800 ml blood.

4 IV.2 AB

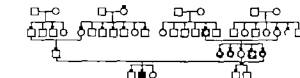
Nose-bleeding — At 8 years severe nose-bleeding and vomiting of blood during common cold. Patient *died* from bleeding despite blood infusions.

Joints — At 4–6 years joint bleedings, particularly in knees and ankles. Right knee ankylotic.

Family 5



Family 6



6 IV 2 RF

Trauma. — Often large soft tissue haemotomas after trauma. Cuts followed by profuse bleeding. After a trivial contusion of the neck when patient was 6 years, Hb fell to 9.0 g/100 ml. At 4 years bleeding from wound of cheek persisted until after infusion of fresh blood.

Prick of fingertip for blood sampling during infancy followed by obstinate bleeding.

After puncture of femoral vein, when patient was $1^1/_2$ years old, large haematoma in groin and stasis of entire leg. Bleeding ceased after administration of 100 ml F I-O.

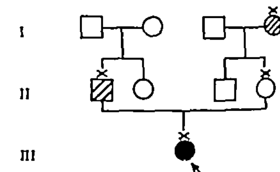
Joint — At 8 years effusion of left knee. Treated with 200 ml F I-O and 3x250 ml fresh plasma. Improved. — At 12–13 years pain and swelling of ankles, especially left ankle. Better following infusion of fresh plasma. Roentgen examination showed that cartilage in upper part of the joint between talus and naviculare was somewhat thin. — Persistently reduced mobility of left ankle.

Intramuscular and subcutaneous bleeding — At 12 years tenderness and pain of calf and thigh muscles. Bleeding suspected. 2x100 ml F I-O was given, after which pain ceased.

At 13 years large, fairly superficial swelling of soft tissue in right upper gluteal region. Patient received fresh plasma, all together 1 400 ml. Improved.

Bleeding after puncture of femoral vein: see above under trauma!

Family 7



7 III 1 MA

Traumatic oral bleeding — At 20 months after a fall obstinate bleeding for more than one week from wound on the underneath side of tongue. Hb fell to 5.6 g/100 ml. Patient received blood infusions.

Urine — At 5 years dark-red urine during passage of two stones. — At 23 years gross haematuria with passage of blood clots. Hb 12 g/100 ml. Urography normal. Patient treated first with 2 infusions of fresh blood to staunch bleeding. Improved. At recurrence after a week fresh plasma, 400–600 ml a day was infused and ε-ACA, 5 g.x4 was given for 7 days. Bleeding then ceased and did not recur.

Menstruation. — Menarche at 11 years. During following half year often profuse menstruations. Hb once fell to 4.1 g/100 ml and afterwards often to about 5 g/100 ml. Patient received several blood infusions. Successful treatment for 1 year with progesterone preparation (Progestin® Pharmacia) 3x5 mg in 2-week periods at end of menstrual cycle. Ergotamine-ergometrinmetartrate (Neo-Gynergen® Sandoz) and adrenon-chloride (Styphnon® Chemosan) also given as soon as bleeding started. Menstrual bleeding less profuse also after withdrawal of progesterone.

At 13 years menorrhagia, which was treated with ACTH and cortisone (Fig. 19) but without convincing effect on the menstrual flow.

Intracranial bleeding — At 3 years subdural bleeding after $2^1/_2$ m fall from slide. Op. See below

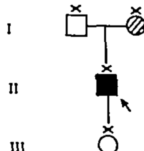
Tooth extraction. Teeth extracted under protection of blood infusion. No notes about any bleeding

Intracranial op — At 3 years subdural bleeding (see above). Op with removal of dark blood and clots. Some hours afterwards profuse bleeding from op-region and signs of incipient shock. Blood infusions given. No further bleeding observed but 5 days later Hb was only 7.2 g/100 mL.

II.1 O.A.

Pleural bleeding — At 53 years after rib fracture pneumothorax and fluid level conceived as bleeding. At op. 2 months later adhesions, which were loosened. No haematoma was found.

Family 8



8 II.1 RB

Haematoma. — Always bruised readily. Hospitalized at 22 years because of large haematoma on posterior thigh without known previous trauma. Hb 11.7 g/100 mL.

Joints — From 14 months of age often recurrent joint bleeding following trivial trauma or without known preceeding trauma, most in knees but also in left hip, left ankle and right elbow. Roentgen showed severe reduction of cartilage in several joints as well as destruction, particularly in distal parts of femur and in both patella. Changes of type seen in haemophilia. Reduced mobility and deformation of several affected joints. Patient walks with a limp. Patient often received infusions i.v. of fresh blood and fresh plasma, 400–1,600 ml, to stop or prevent bleedings. On one occasion he was given 100 ml F I-O. Signs of hepatitis once after plasma infusions (See below).

At 43–44 years used AMCA 0.5 gx2 daily for more than a year. No new joint bleeding during this treatment.

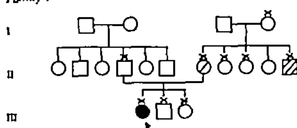
Hepatitis. — At 40 years, some months after infusion of fresh plasma because of joint bleeding, patient showed signs of hepatitis. Bilirubin increase to 18.5 mg/100 ml, GPT max. 558 U and thymol ext. max. 16 U. One month later much improved.

9 III.1 E.S.

Urine — At 15 years gross haematuria. Hb fell to 7.5 g/100 ml. Urography revealed nothing remarkable. At 26 years recurrence of haematuria.

Menstruation — Menarche at 12 years. Menstrual bleedings first profuse, later normal. During the last few years used "p-pills

Family 9

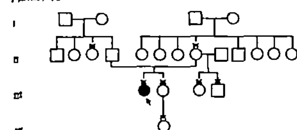


Joints — Since 7 years of age recurrent joint bleedings in ankles, right knee, right hip, right elbow and, in adult age, also in right wrist. Roentgen examination showed considerable destruction of cartilage and articular surfaces in deformed right elbow and right knee. Range of mobility of the knee and elbow was reduced. Infusion of fresh plasma on various occasions to stop joint bleeding.

Post-extraction haemorrhage — Oozing post-extraction haemorrhage usually for at least a week.

At 20 years tooth extraction under protection of 450 ml fresh blood and 6x400 ml fresh plasma. Received 2 bottles of blood because of later bleeding.

Family 10



10 III.1 MCA

Gastro-intestinal — At 18 years bleeding ulcer for which patient received blood infusions on several occasions. At 25 years abdominal pain and melaena. Hb 7.5 g/100 ml. Roentgen examination showed deformation by ulcer but no crater. Received 2 bottles of blood. — At 32, 34 and 36 years melaena. Hb once fell to 6.9 g/100 ml. No roentgen examination. On these occasions blood transfusions were given immediately to replace blood loss, thereafter F I-O was infused: 500, 1,900, and 400 ml, respectively. Bleeding soon ceased during treatment.

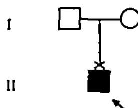
Ovaries. — At 25 and 28 years attacks of abdominal pain and sensation of fullness of small pelvis. Hb fell to 9.1 and 5.1 g/100 ml, respectively. Bleedings from ruptured ovarian cysts were suspected. Treated with blood infusions, on last occasion also with 200 ml F I-O.

During temporary withdrawal of "p-pills" at 35 years patient had similar attacks of intermenstrual pain, and a fist-sized infiltrate was palpated to the right behind the uterus. Treated with 800 ml of F I-O. Also ε ACA, 4 g.x5 was given for 4 days. Improved.

Pleural bleeding — At 25 years after bleeding from a ruptured ovarian cyst effusion into left pleura, haemothorax. Treated with pleural puncture under protection of F I-O without abnormal bleeding.

Uterine curettage — At 19 years uterine curettage because of meno-metrorrhagia. After curettage the bleeding became worse and Hb fell in 4 days from 7.5 to 4.5 g/100 ml. Patient received several bottles of blood. Bleeding did not cease until after injection of ergotamine-ergometrinetartrate (Secatotal® Astra).

Family 11

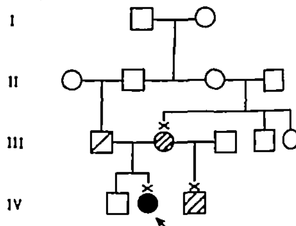


11 II.1 GB

Gastro-intestinal — At 30 and 31 years gastro-intestinal haemorrhage — given 3 bottles of blood on second occasion. At 44 years melaena twice. Hb once fell to 5.3 g/100 ml. Roentgen examination showed gastro-duodenitis, otherwise nothing remarkable. Patient received 9+14 bottles of blood. — From 51 years of age melaena repeatedly at intervals of 0—3 months. Repeated roentgen examination of oesophagus, stomach and duodenum and colon revealed nothing remarkable. Received numerous infusions of F I-O and packed red blood cells. When given ordinary blood transfusions the patient reacted with fever which was abated by prednisolone. Also given ε-ACA (5 gx4 a day) and later AMCA (1 gx2 — 2gx4 a day), but with only limited effect on the bleedings. Neither did prednisolone in a dose of 30 mg per day produce any effect. Patient granted a sick-pension because of gastric bleeding and continuous anaemia. Finally operated upon to find source of bleeding (see below).

Explorative abdominal op — In view of the disabling gastrointestinal bleedings of unknown source the patient was subjected to extensive abdominal surgery and laparotomy. The operation was performed under protection of F I-O immediately after a long spell of bleeding from the digestive tract. The patient was in a poor state of nutrition because of narcomania. Serum protein only 4.3 g/100 ml. Praeop. the patient was given F I-O 300+300+500 ml. The AHF-values reached a high level: over 200 / (Fig. 7). Gastroscopy and enteroscopy during op. revealed mucosal haemorrhage. No bleeding was noticed in the op field ascribable to surgery. The patient was given 2 bottles of packed red blood cells during op. Intense therapy with F I—O was continued after op. all together 1 800 ml on first 2 days and then about 2x200 ml a day. The AHF level was always above 100 / . The bleeding time according to Duke was normal on the day of op. and the first few days afterwards, but on the 5th to 8th day after op. it rose to more than 30 min. despite treatment. During these 4 days the patient bled profusely from the rectum and there was some oozing from the op.-wound. He was given 2,300 ml of packed red blood cells. The dose of F I—O was increased from about 2x200 to 3x200 ml a day. The bleeding time then became normal and the bleeding ceased. Antihaemorrhagic prophylaxis was continued for a month.

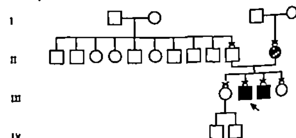
Family 12



12 IV.2 KPA

Menstruation — At 15 years profuse menstrual bleedings, which were controlled with ergotamine-ergometrinetartrate(Secatotal® Astra). At 19 years very profuse menstrual bleedings with Hb down to 5.2 g/100 ml. The bleedings ceased after treatment with ε-ACA and blood transfusions. Gynaecological consultation revealed no local cause of the bleeding. Long-term treatment was started with "p-pills" with good effect on the menstrual bleedings.

Family 13



13 III.2 SE

Nose-bleeding — Frequent nose-bleeding in childhood, especially during common colds. At 6 years patient had nose-bleeding after op. because of mastoiditis. Hb fell to 4.5 g/100 ml. Blood infusions given. — At 17 years successful treatment for nose-bleeding with AMCA, the bleeding stopped after 6 hours.

Ear — At 6 years bilateral otitis and anaemia with Hb down to 5.6 g/100 ml.

Urine — From 14 to 27 years gross, but generally not severe, haematuria, every year or every other year. Urography revealed nothing remarkable. Cystoscopy showed mild bleeding from the bladder neck. On some occasions treated with fresh plasma, at most 7x400 ml with good effect on bleeding. At 34–35 years taken AMCA, 0.5–1 gx2 a day when he had episodes of haematuria and then did not need hospitalisation.

Intramuscular bleeding — At 33 years swelling of left calf after having been run into by a mopedist. Treated with fresh plasma and F I-O. The swelling soon disappeared. About 4 months later signs of hepatitis (see below).

Post-extraction haemorrhage — At 11 years severe post-extraction haemorrhage. Given 2–3 bottles of blood. — At 22 years tooth extraction under protection of fresh blood, 1 bottle before and 1 immediately after op. Severe bleeding, worst on the 6th day after op. Given all together 31 bottles of blood and 2 infusions of fresh plasma within 1 month.

At 23 years tooth extraction under protection of F I-O fresh plasma and fresh blood. After 200 ml of F I-O the bleeding time (Duke) was still more than 40 min. AHF 150 %. *Tooth extraction was not followed by* any bleeding complication. — That year further teeth extracted under protection of 200 ml F I-O before op and 10 infusions of fresh plasma within 4 days after op. Only mild bleeding at op. 8 days later profuse bleeding from extraction wound. Better after treatment with blood and fresh plasma. During 4 weeks in hospital patient received all together 4 blood infusions and 20 infusions of fresh plasma.

Op behind the ear — At 6 years the patient was operated upon because of mastoiditis behind left ear. Profuse bleeding from the op. area for several days. At the same time he had nose-bleeding and bleeding from behind the left tonsil. Hb 2 days after op 4.8 g/100 ml. Blood infusions given.

Hepatitis. — At 33 years, about 4 months after treatment with fresh plasma and F I-O (see above under intramuscular bleeding) the patient developed signs of hepatitis. Bilirubin increased to 1.5 mg/100 ml. GPT max. 231 U. Thymol ext. max. 4 U.

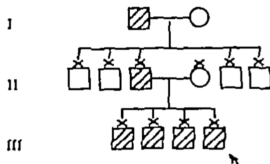
III.3 J.L.E.

Intracranial bleeding — At 14 years head injury from fall from cycle. He had headache, vomiting and retrograde amnesia. Skull X-ray revealed nothing remarkable. On the first few days after the accident the patient was somewhat cloudy but otherwise in a satisfactory general condition. 6 days after the accident he became increasingly sluggish and after a further 2 days he *died*. Post mortem examination revealed a haematoma, the size of a hen's egg in the right frontal lobe and small subdural haemorrhages.

14 III 4 LJ

Joints — At 8 years he fell and hit his right knee, which swelled diffusely and was tender. Immobilisation of the knee in plaster for 10 days.

Family 14

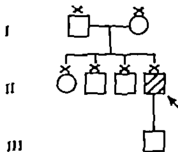


14 II.3 BJ

Oesophageal bleeding — Cardiospasm. At 35 years coffee-ground vomiting. Hb 10.2 g/100 ml.

Op on oesophagus. — At 35 years operated upon because of cardiospasm without immediate bleeding. The pleura was opened. First week after op. haemothorax. Repeated pleural puncture produced 600 + 850 + 600 + 300 ml. Received 9 bottles of blood.

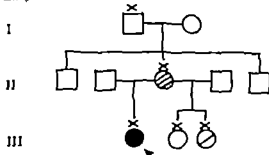
Family 15



15 II:4 KS

Urine — At 28 years gross haematuria on several occasions. Urography showed on first occasion a cavity in the calyx in the middle part of the left kidney. One week later the change had disappeared.

Family 16



16 III 1 AKZ

Nose-bleeding — From 3 to 10 years repeatedly hospitalised because of nose-bleeding, received at least 8 bottles of blood. At 15 years troublesome nose bleeding after hysterectomy: nosebleeding treated with

tamponade. At 16, 17 and 19 years nose bleeding with Hb down to 8.5 g/100 ml. On one occasion concomitant ovarian bleeding. Patient given blood infusions and on 2 occasions F I-O

Tooth shedding — At 8 years given 2 bottles of blood because of bleeding from loosening tooth.

Menstruation. — Menarche at 12 years. First 4 menstrual bleedings very profuse and required repeated infusions of fresh blood and fresh plasma, which, however did not normalise the bleeding time (Duke). At 3rd menstruation the patient received progesterone, after which bleeding gradually ceased. But during treatment the patient developed haematuria and haemarthroses. Despite 4 infusions of plasma she also had severe haemorrhage in the floor of the mouth. Fever 40 C. Patient received 5x200 ml F I-O with good effect. AHF-level and bleeding time became normal. The patient soon improved. Progesterone afterwards replaced by methyltestosterone: 5 mg every other day. This kept menstrual bleeding normal, which, however increased on temporary reduction of the dose of methyl-testosterone. After 3 years treatment the patient was fairly virilised. Temporary withdrawal of treatment resulted in 2 severe menstrual bleedings requiring treatment with fresh plasma and F I-O. Hysterectomy was therefore decided upon (see below).

Ovaries. — At 16 years (1 year after subtotal hysterectomy) hospitalised twice because of abdominal pain and signs of haematoma in lower part of abdomen. Bleeding in association with discharge of ovum suspected. Simultaneous nose-bleeding. The patient repeatedly received infusions of F I-O 1 700 ml within 15 days. Treatment with "p-pills" started with good effect on the bleedings. However during treatment signs of impaired liver function appeared with slightly raised values for GPT viz. 55–71 U. Treatment with AMCA 1.5 gx2 for 2–3 days was tried at the time of but the patient developed abdominal pain, which prevented effective continuation of treatment.

Bleeding in floor of mouth. — At 12 years following severe menorrhagia (see above) and numerous blood infusions the patient also bled from the tissues around a carious tooth. The bleeding spread to the floor of mouth and downwards and threatened to obstruct larynx and trachea. The patient then received 5x200 ml F I-O with good effect on the bleeding.

Hysterectomy — At 15 years, after the patient had been treated for 3 years because of menorrhagia (see above) with testosterone preparation, she had such signs of virilisation that hysterectomy was decided upon. Subtotal hysterectomy was performed under protection of F I-O: 550 ml before and immediately after op. (Fig. 6, page 121). The appendix was removed *en passant*. Loss of blood at op. normal. After op. the patient was given freezedried F I-O: 150–200 ml day for 2 days and the first 4 days after op. were uneventful.

On the 5th day after op. the AHF alone had fallen to 10 %. That day the patient began to bleed profusely through the portio to the vagina. The vagina was evacuated of about half a liter of clots, after which a tamponade was inserted. But the patient continued to bleed profusely for 5 days despite local tamponades and administration of 300–400 ml F I-O a day. Immediately after infusions AHF increased to over 100 but then rapidly fell to 21–24 . Addition of patient's plasma 1/10 to normal plasma caused a slight prolongation of the recalcification time (up to 10) as a sign of the presence of circulating anticoagulant. The patient repeatedly received blood infusions. Because of the bleeding cervical cerclage was performed 10 days after op. and during the following weeks the patient improved. Continued treatment with 100–450 ml F I-O a day. 23 days after op. the patient again began to bleed severely from the vagina. The same day she also had nose-bleeding which was successfully treated with tamponment with oxidized cellulose (Oxycel® Parke & Davis). Vaginal bleeding gradually ceased. F I-O withdrawn. The patient spent 2 months in hospital during which time she received 10,785 ml F I-O as well as 11 bottles of blood, mostly fresh blood. She was sent home in a good general condition.

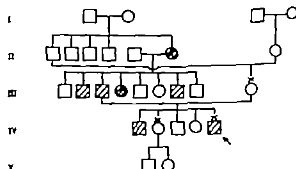
3 months after discharge from hospital the patient developed signs of hepatitis.

Retroperitoneal bleeding — At 10 years after trauma with consequent effusion in right hip joint the patient also had a lump in the lower part of the abdomen. Roentgenography: psoas-contour diffuse. She developed temporary neurological symptoms: paresis, impairment of sensibility and disturbed reflexes of right leg.

Anticoagulant — At 19 years examined with refined test for anticoagulant. With the patients plasma neutralisation obtained of 62 of AHF in corresponding amount of normal plasma.

Hepatitis. — At 16 years — 4–5 months after she had received intense treatment with blood, plasma and F I-O after hysterectomy — the patient developed signs of hepatitis. GPT max. 2,480 U. Rapid improvement.

Family 17



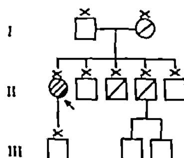
17 II.6 KL

Pulmonary haemorrhage — Said to have *died* from pulmonary haemorrhage.

17 III 4 AL

Pulmonary haemorrhage — Said to have *died* from pulmonary haemorrhage.

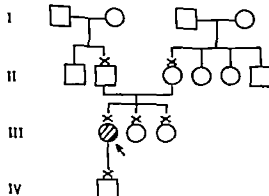
Family 18



18 II.1 VÅ

Cholecystectomy – At 45 years cholecystectomy under protection of F I-O and fresh plasma. 300 ml of F I-O and 400 *ml fresh* plasma given before op. *AHF* value on op. day 77 % and bleeding time according to Duke then 5 min. 20 sec. No abnormal bleeding at op. First 2 days after op. the patient received all together 550 ml of F I-O and 1,200 ml fresh plasma. AHF value 165,50 and 50 %. Bleeding time not measured. Profuse bleeding from wound despite treatment. Given 2x1,000 ml blood and further 600 ml F I-O and 400 ml fresh plasma on 3rd–4th day after op. Op. wound resutured. Bleeding then stopped.

Family 19



19 II.1 SA

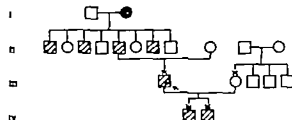
Menstruation. – Menarche at 12 years. The following years the menstrual flow was profuse. At 14 years the patient was hospitalized after uterine curettage (see below) because of menorrhagia and then Hb fell to 3 0 g/100 ml. Given 1 blood transfusion. After parturition at 19 years the menstrual flow was less profuse.

Parturition. At 19 years. Loss of blood at parturition 800 ml. 4 hours later oozing of blood, which became worse. 15 bottles *of blood given* within 3 days. Bleeding stopped for one day then recurred. 2 bottles of blood given. Bleeding stopped for 9 days and then recurred, though not profuse and persisted for several weeks. Patient received 4 further bottles of blood and fibrinogen. Bleeding gradually stopped.

Exaeresis uteri. – At 24 years pregnancy was interrupted in mens II with exaeresis instrumentalis. Patient received 1 bottle of fresh plasma before op. She began to bleed the same day. Moderate bleeding after op. The patient received a further bottle of blood and during the following week all together 8 bottles of fresh plasma. She nevertheless began to bleed again, though mildly 1 week after op. Hb 10 7 g/100 ml. Bleeding continued for about 1 week and the patient received a further 4 bottles of blood. Hb afterwards 14.7 g/100 ml.

Uterine curettage – At 14 years uterine curettage because of menorrhagia. After about a day she again began to bleed worse than before and she was admitted to hospital. (See above under Menstruation).

Family 20



20 IV.2 KGP

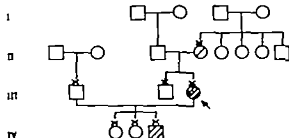
Ear – At 2 years haematotympanon and concomitant nose-bleeding.

Post-extraction haemorrhage – At 20 years extraction of +8 without abnormal loss of blood at op. – 3–5 days later increasing bleeding, which ceased after *tamponade and suture*

Some months later extraction of +3 under protection of fresh blood. 1 bottle before and 1 bottle after op. Nevertheless bled during postop. course and received a further 2 bottles of fresh blood.

Extraction of –6 at 21 years. Given 1 bottle of fresh blood before and 1 after op. Nevertheless bled again 1 week after op. for which reason a further 2 bottles of fresh blood were given.

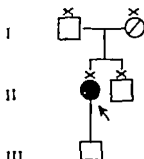
Family 21



21 III.3 MÅ

Menstruation. – Menstrual bleedings always profuse, especially after last parturition, when patient was 22 years. During the following years obstinate anaemia with Hb about 10 g/100 ml. At 27–28 years all together 4 blood infusions. Finally hysterectomy

Family 22

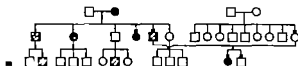


22 II 1 ID

Nose-bleeding — From 1 to 9 years of age often treated because of nose-bleeding. Hb on one occasion at 1 year 7.2 g/100 ml, at 9 years, 10.9 g/100 ml. — At 25 years a few months after withdrawal of treatment with "p-pills" nose-bleeding with shock. Given all together 10x100 ml F I-O 10 bottles of blood and 10 of fresh plasma within 9 days.

Menstruation. — Menarche at 12 years. First years very profuse menstrual flow Admitted to hospital at 12–13 years and at 15 years. Lowest Hb 7.6 g/100 ml. On first occasion the patient received infusions of fresh plasma with good effect.

Family 23



23 III 12 KW

Tonsils. — From 1 to 8 years of age frequent profuse bleeding in association with throat infections, first years the blood appeared to come from the mucosa of the throat, but from 3 years of age it was found to come from inflamed tonsils. At 8 and 10 years life-threatening tonsillar haemorrhages with Hb down to 5.2 g/100 ml. Treated with blood infusions and F I-O 200 ml each time. — Tonsillectomy finally decided upon (see below).

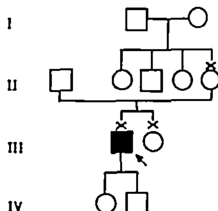
Tonsillectomy — At 10 years tonsillectomy under protection of F I-O 400 ml before and 1,600 ml within 11 days after op. No abnormal bleeding.

II:4 S.W

Ovaries. — At 19 years severe abdominal pain during menstruation. Hb 8.3 g/100 ml. Laparatomy revealed a large haematocele (See below)

Op of ovarian cyst — At 19 years operated on because of severe abdominal pain and anaemia (see above under ovaries). Laparatomy revealed around the right ovary a large haematocele, extending up to umbilical plane. Old clots removed Salpingo-oophorectomy with peritonealisation. Obstinate oozing of blood from the wall of the haematocele, which was very rough. Miculicz duct was inserted as well as a fairly large tamponade. In the later course the patient repeatedly went into shock and despite blood transfusions *died* 2 days after op. — Also subcutaneous bleeding around op wound.

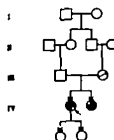
Family 24



24 III.1 RA

Nose-bleeding — Troublesome nose-bleedings since childhood, especially during physical exertion and after trauma of the nose. At 3 years and 13 years treated with tamponade.

Family 25



25 IV 1 GL

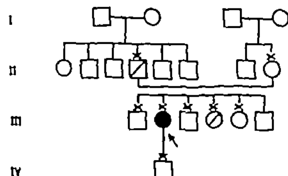
Op because of trigeminal neuralgia. — At 41 years op. because of trigeminal neuralgia with division of the root. Local bleeding in op. area and extradurally produced symptoms after half a day and required evacuation on two occasions. Persistent neurological symptoms *viz* double vision and disturbed balance.

26 III.2 EF

Nose-bleeding — At 7 months nose-bleeding for 2 days after blow on nose. At 2, 4 and 6 years bleeding from tonsils and nose. The patient received 5 bottles of blood. Admitted to hospital at 15 and 20 years because of nose-bleeding.

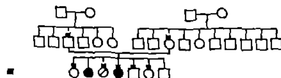
Parturition. — Delivery at 26 years. The patient then received 2x100 ml F I-O and on the following days 2 bottles of fresh plasma. No abnormal bleeding at par-

Family 26



turition or during the first few weeks afterwards. Uterus well involved. 3 weeks after parturition increasing vaginal bleeding. Hb fell from 12.3 to 10.8 g/100 ml. The following week the patient was treated with methylergometrine (Methergin® Sandoz), "p-pills" and ε ACA (6 g×4 a day). Furthermore, she received F I-O 100+100+400 ml, 450 ml fresh plasma and 650 ml fresh blood. But bleeding continued and Hb fell to 8.4 g/100 ml. Finally instrumental evacuation of the uterus with removal of clot and pieces of decidua. Histological examination showed chronic, non-specific endometritis with decidual rests. Bleeding ceased after op.

Family 27



27 III.4 KR

Menstruation. — Menstruation always profuse. Between 15 and 26 years admitted to hospital on all together 10 occasions. Hb once as low as 4.5 g/100 ml. On every occasion the patient received one or more bottles of blood. At 26 years when bleeding had sometimes been life-threatening, roentgen castration.

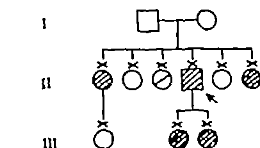
Ovaries. — On 5 occasions, including 2 at 23 and 24 years, severe abdominal pain and feeling of lump or tension in small pelvis. Symptoms appeared on one occasion after abdominal palpation. The patient once required blood transfusions. These episodes were regarded as symptoms of bleeding from ruptured follicular cysts.

Joints. — Since childhood repeated joint bleeding, mostly in right knee, sometimes also in left ankle and right hip. Impaired range of movement, above all, of right knee. At 43 years range restricted to 170°–80°. X-ray showed considerable reduction of cartilage, uneven joint surfaces and periarticular rarefaction. Changes of the same type as seen in haemophilia.

Cholecystectomy — At 48 years operated upon with cholecystectomy + choledocholithotomy + drainage. Op. under protection of F I-O 500 ml before and 5,100 ml during 3 weeks after op. The patient bled diffusely in the op.-field and received one blood transfusion. No abnormal postop. bleeding.

Uterine curettage — Repeated curettage because of menorrhagia. At 19 years curettage followed by profuse bleeding with Hb down to 3.5 g/100 ml. Several blood transfusions.

Family 28

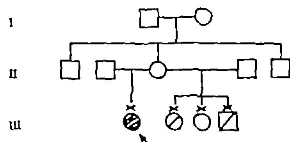


28 II 4 AS

Post-extraction haemorrhage — At 47 years tooth extraction twice under protection of F I–O, 1 400 and 1 100 ml, respectively (Fig. 15). First extraction of 7 lower teeth, then of 5 upper teeth. On first occasion no abnormal bleeding. On second fairly abundant bleeding, when F I-O had been used from large batches with fresh frozen plasma as a basic material and which had been allowed to stand over night during preparation. Hb fell from 13.6 to 11.2 g/100 ml.

Op. because of gynaecomastia — At 44 years operated upon because of gynaecomastia. During postop. course blood oozed from op. area. Large haematoma removed the day after op. Hb fell to 10.9 g/100 ml. The patient received 1 bottle of blood.

Family 29

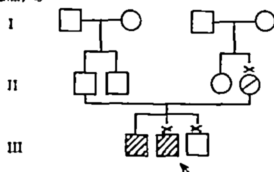


29 III.1 IOK

Op. on ear — At 34 years operated upon because of otosclerosis. Mild bleeding from auditory duct after op. — Result of op. poor probably because of bleeding.

At 41 years stapedectomy under protection of F I-O 200 ml before and 200 ml after op. No abnormal bleeding. Hearing improved. Improvement still maintained at control one year later.

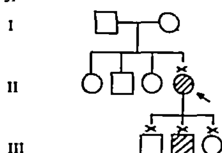
Family 30



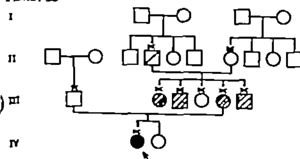
30 III.1 ÅW

Nose-bleeding. — At 7 years nose-bleeding during measles, with shock and *death* within one day.

Family 31



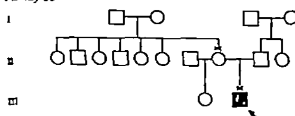
Family 32



32 IV 1 AJ

Haematoma. — Since 4 months of age readily even after trivial trauma, *e.g.* when she hit the side of the bed.

Family 33



33 III.2 AR

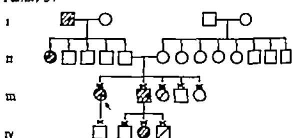
Gingival bleeding. Tendency to gingival bleeding since childhood, worse once after tooth extraction at 17 years. Sometimes awoke in the morning with mouth full of blood.

Trauma. — After blood sampling from ear at 7 years bleeding persisted until after blood transfusion.

Post-extraction haemorrhage. — Profuse at 17 years. 2 bottles of blood were given.

At 20 and 24 years tooth extraction on 2 occasions under protection of F I-O all together 1,500 ml and 300 ml, respectively. Last time also given fresh plasma, all together 4,600 ml. On first occasion given F I-O, prepared in a modified way. Rather profuse bleeding which was, however, controlled by local treatment. On second occasion only little bleeding.

Family 34



34 III.2 IL

Gastro-intestinal. — Occasionally ulcer-like symptoms since 28 years of age and on at least one occasion roentgenologically verified duodenal ulcer. At 40 years operated upon with gastric resection. During following years he had haematemesis and/or melaena on at least 5 occasions. X-ray of stomach and duodenum on those occasions revealed no crater with certainty. Patient often received blood, on one occasion 20 bottles. At 45 years severe gastro-intestinal bleeding and shock. The patient first received blood followed by F I-O, 3x100 ml within 3 days. No more F I-O available at that time. Bleeding continued and the patient *died* a few days after onset. Autopsy showed changes suggesting callous gastric ulcer. Autolytic changes made examination difficult.

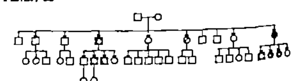
34 I.1 KL

Gastro-intestinal. — Patient said to have *died* from gastric bleeding.

34 II.1 HE

Gastro-intestinal. — Patient said to have *died* from gastric bleeding.

Family 35



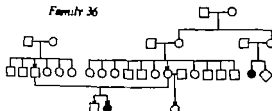
35 II.4 PT

Post-extraction haemorrhage. — At 55 years severe bleeding after extraction of wisdom tooth.

Later that year extraction of second wisdom tooth under protection of 500 ml F I-O without abnormal bleeding. — At 56 years op. of wedged in 3rd molar and

extraction of 2 molars under protection of all together *1,800 ml F I-O. Despite F I-O relatively profuse blee*ding from op. area. Only little effect on AHF level and bleeding time and the patient s blood was found to contain *increased anti AHF-activity* – Tooth extraction at 58 and 59 years under protection of F I–0 (Fig 16) 700 and 1 100 ml, respectively No abnormal bleeding despite poor effect on level of AHF in patient s blood.

Family 36



36 IV.2 IL

Parturition. – At 20 years delivery under protection of F I–0 (Fig 9). – AHF in patient s blood 3 weeks before delivery 4.8%. Shortly before delivery the patient received F I–O, 2x200 ml and fresh plasma, all together 1,050 ml. AHF-level rose to 125 ‰ but bleeding time (Duke) remained prolonged: more than 30 min. Delivery – vacuum extraction after stimulation with Syntocinon drip. On division of shoulders the patient received methylergometrine (Methergin® Sandoz) On expulsion of placenta fairly abundant bleeding, about 900 ml After parturition the patient received further 300 ml of F I-O During the following weeks given 800 – 1,000 ml fresh plasma a day Despite treatment and satisfactory AHF-levels 44 95 ‰ bleeding time (Duke) was repeatedly prolonged, more than 30 min. and the patient continuously had menstruation-like bleeding 14 days after parturition, by when AHF had fallen to 12.5 ‰ bleeding was profuse The patient received extra doses of fresh plasma, as well as 600 ml of blood and later further 200 ml of F I-O Improvement. New episodes with increased bleeding up to 1,000 ml each time 23 and 44 days *after parturition* Instrumental evacuation of uterus on both occasions, yield on first occasion interpreted as placental rests Also on these occasions the patient received extra doses of F I-O 100 – 200 ml From 45th day after parturition the patient was given 100 – 200 ml F I-O a day for 14 days and had no further bleeding

The *infusions of fresh plasma* were repeatedly *followed by allergic urticaria*

Joints. – During childhood occasional swelling of the knee, probably joint bleedings

III 19 K.B

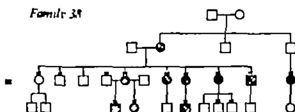
Menstruation. – Menarche at 14 years According to hospital records, patient had until then been healthy

Vaginal bleeding continuously during following months and *death* 5 months later during an exacerbation with bleeding also from the nose, mouth and intestines Records contained no notes about platelets, bleeding time or coagulation time

38 IV 4 KS

Menstruation. Menarche at 12 years. First 4 years

Family 38

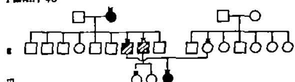


profuse menstrual flow Hb fell to minimum of 8 9 g/100 ml At 16 years patient received infusions of fresh *plasma* regularly for 6 months with good effect on bleeding tendency But treatment was then stopped because of *transfusion reactions with urticaria and swelling in throat* Now receives p-pills and menstruation less profuse.

38 III.7 EP

Haemoptysis – Treated at sanatorium for pulmonary tuberculosis at 22 – 23 years and at 44 years Cavity on last occasion The patient had mild episodes of haemoptysis

Family 40



40 III 3 AMW

Traumatic oral bleeding – At $1^1/_2$ years bleeding from lip-bite after fall. Admitted to hospital after 2 days, Hb then 10 3 g/100 ml. Continued to bleed, developed signs of shock and was given 2 bottles of fresh blood. – At 2 and 4 years prolonged bleeding from small sores on tongue

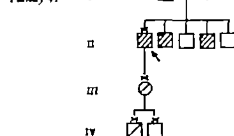
Ear Deaf on one side and impaired hearing on other Not had otitis Impairment of hearing possibly caused by middle ear bleeding.

Subcutaneous or intramuscular bleeding – At 8 years *admitted to hospital because of fluctuant orange-sized* swelling in right gluteal region after fall. Hb 11.3 g/100 ml Given 100 ml F I-O and 200 ml fresh plasma and the swelling disappeared.

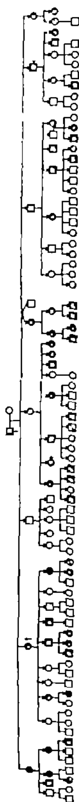
40 I 2 GW

Gastro-intestinal Said to have *died* at home from gastric haemorrhage No autopsy

Family 41



Fam 4



42 II.2 GÅ

Nose-bleeding and miscarriage — At 31 years miscarriage with heavy loss of blood. Simultaneous nose bleeding. Hb fell to less than 10 ⁄ according to Sahli (normal 80—100 ⁄) and erythrocytes down to 960 000/mm³

42 III 19 IH

Parturition. — Bleeding at delivery at 27 years 1,200 ml; at 29 years, 600 ml (patient had on last occasion received oxytocin (Utedrin® Astra) and secale). Delivery at 23, 25 and 35 years without abnormal bleeding. — During pregnancy at 24 and 35 years, the bleeding time (Duke) became normal in mens IV and mens III, respectively

Hysterectomy — At 50 years hysterectomy because of uterine myoma. 400 ml F I-O was given before and 400 + 100 ml during the first 2 days after op. Patient received simultaneously 9 gx5 of ε-ACA a day i.v. She bled rather profusely during op but the bleeding could be stopped by ligation and suturing. The patient received 2 bottles of blood. One week after op. bleeding again began but ceased after re-administration of F I-O all together 600 ml within a period of 5 days. The patient received a further 2 bottles of blood.

Uterine curettage — At 50 years uterine curettage + diagnostic biopsy of portio. About one week after op profuse bleeding, for which the patient received 1 bottle of blood and 200 ml F I-O

III.20 BN

Pleural puncture and thoracocentesis — For several years the patient was treated with pneumothorax because of pulmonary tuberculosis. When filling the pneumothorax at 23 and 24 years on a couple of occasions haemothorax. On one occasion after thoracocentesis an orange-sized extrathoracic haematoma. At 24 years the patient was admitted to hospital because of haemoptysis. Thoracocentesis produced thick blood The patient *died* the following day

III.21 S N

Nose-bleeding — After tooth extraction.

III.25 S.N

Nose-bleeding — Often in childhood and adolescence, once at 7 years after tooth extraction when the patient fainted. Cauterised, on last occasion at 22 years.

Joints — At 14 and 17 years haemarthrosis of left and right knee, respectively after trauma and *joint puncture* On latter occasion Hb fell from 11.2 to 7.0 g/100 ml. Patient received blood infusions. No permanent joint deformity

42 III.27 KZ

Parturition. — After second delivery at 31 years profuse prolonged bleeding from a large vaginal rupture. The rupture was sutured, but the bleeding continued for a week. The patient received 6 bottles of blood.

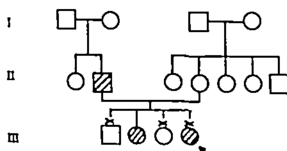
42 III.33 BAA

Eye-bleeding. — At 28 years after trauma troublesome intraocular bleeding, which disappeared within 5 days treatment with fresh plasma, 400 ml a day

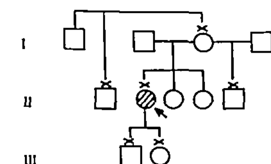
42 III.34 KS

Menstruation. — Menarche at 13 years. Profuse prolonged bleeding at 3rd menstruation, received 2 bottles of blood. Curettage without effect. Bleeding ceased after treatment with chorion-gonadotropin (Pregnyl® Pharmacia). During the next few years menstrual flow irregular and profuse. Patient admitted to hospital again at 16 years because of menorrhagia, which ceased after curettage. Less copious menstruations after parturition at 18 and 20 years.

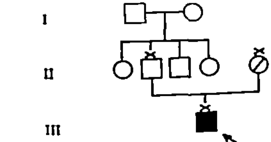
Family 43



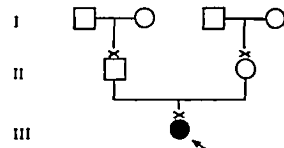
Family 44



Family 45



Family 48



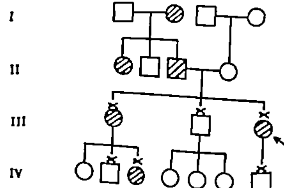
48 III.1 BH

Trauma. — At 7 years hit right knee. Bleeding from wound, which became worse after some hours. Hb that day 8.0 g/100 ml, some days later 6 7 g/100 ml. Patient treated with 2x100 ml F I-O and 200 ml blood after which bleeding ceased.

Joints. — Since 1 year of age trivial trauma caused swelling, pain and impairment of movement of various joints: ankles, knees, elbows and sometimes also wrists. Hb on one occasion during such symptoms 10.0 g/100 ml. Otherwise no anaemia. The symptoms were interpreted as joint bleedings. Range of movement of left elbow permanently reduced. — Roentgen examination showed somewhat deepened joint surface of left elbow otherwise nothing remarkable. — Treated on some occasions with F I-O 100—300 ml each time. Once she developed signs of hepatitis 3—4 months later (see below)

Hepatitis. — At 7 years, 3—4 months after infusion of F I-O signs of hepatitis appeared with mild icterus and increase of GOT to 170 U. Soon improved without treatment.

Family 49



49 II.3 AA

Intracranial bleeding. — At 68 years fall from moderate height without loss of consciousness. Same the clinical symptoms of cerebral haemorrhage. Examination revealed signs of increased intracranial pressure but not of epi- or subdural bleeding. *Death* with signs of increasing intracranial pressure. No autopsy.

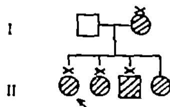
49 III 1 AE

Op of mammae. – At 49 and 53 years operated upon because of mastopathia cystica. On first occasion no abnormal bleeding. After the second op a fist-sized haematoma developed in the op. field. Haematoma incised after 3 weeks with removal of large amount of chocolate-brown, thick fluid. Hb had fallen from 12.2 to 10.5 g/100 ml.

49 IV.3 GS

Parturition. – At 22 years parturition. First hours afterwards mild bleeding from vagina, which ceased after removal of placental part. After 1 week recurrent bleeding, which persisted for several weeks. Hb after 3–4 weeks 6.3 g/100 ml. Patient received 2 bottles of blood. Bleeding continued for several months. Anaemia treated with iron medicine. Histological examination of curettings 6 months after parturition: glandular cystic hyperplasia.

Family 50



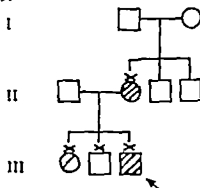
50 I.2 MA

Menstruation. – Menarche at 13 years. Menstrual flow always profuse. Hb at 16 years for several months 9–8.5 g/100 ml, at 22 years once 7.. g/100 ml. On occasion the patient was given 1 blood transfusion. 22–24 years regular injection of choriongonadotropin (Pregnyl® Pharmacia). Menstrual flow became less profuse but since the Hb again fell to 9.1 g/100 ml during menstruation hypophysial implantation was done. No improvement. Patient again admitted to hospital at 26 years because of menorrhagia. Hb then fell to 5.6 g/100 ml and patient was given blood transfusions. At 39 and 40 years menorrhagia and Hb down to 9.0 and 7.3 g/100 ml. On last 2 occasions the patient received 1 blood transfusion each time.

Parturition. – Deliveries at 28, 31, 32 and 34 years. At parturition the patient always bled profusely. After first parturition the patient was given blood transfusion on the second and 6th days. Hb after first transfusion 11.0 g/100 ml, after second 13.1 g/100 ml. 3 weeks after parturition the patient again bled profusely and bleeding continued for 3 weeks, during which the Hb fell to 10.4 g/100 ml. The patient was given a further blood transfusion after which the bleeding stopped. – After the third parturition the patient was given blood transfusion on the second, 5th and 6th day after parturition. Lowest Hb recorded 8.3 g/100 ml (3 days after first transfusion).

Hepatitis. – After treatment with F I-O because of post-extraction haemorrhage the patient had hepatitis with billirubin increase to 5.1 mg/100 ml, GPT 2,000 U and Thymol extinction max 0.64 (normal ≦ 0.10). Patient hospitalised for 1 month and when she left hospital the following values were noted. Serum billirubin 1,7 mg/100 ml, GPT 94 U and Thymol extinction 0,10. She was weak for several months afterwards. Liver function tests gradually became normal.

Family 51



51 III.3 SÅN

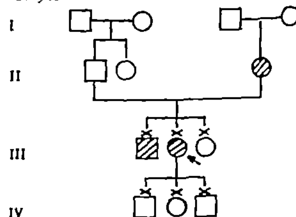
Nose-bleeding. – Frequent nose-bleeding from 2 to 11 years, often requiring hospitalisation. At 10 years Hb fell once to 5.2 g/100 ml. The patient received 5 bottles of blood. At 17 years re-admitted to hospital because of nose bleeding. Subsequent episodes of nose-bleeding less severe.

Op veg ad. – At 6 years curettage of adenoid vegetations. Large adenoid and abundant vegetation removed. Only little bleeding at and after op. Blood values including bleeding time at time of op. said to be normal.

51 II.2 MN

U me – At 50–54 years recurrent haematuria. Removal of polyp in bladder neck did not produce desired effect on bleeding. Repeated urography revealed nothing remarkable. Cystoscopy after op. of bladder neck showed nothing abnormal.

Family 53



53 III.2 IW

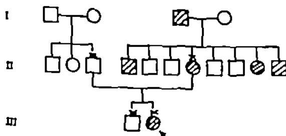
Caesarean section. — At 34 years Caesarean section because of threatened cervical rupture. The first few hours after op. profuse bleeding and shock. No signs of fibrinolysis. The patient received 6 bottles of blood and the following two days 1 bottle on each day. Abnormal bleeding ceased.

53 III 1 SÅ

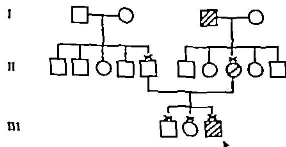
Appendectomy — At 34 years operated upon because of perforated appendicitis. At op. no abnormal bleeding, but 1 bottle of blood was given. Postop. course uneventful.

Gastrectomy — At 28 years gastric resection (B. II). One bottle of blood during op. But no notes about bleeding in hospital records. Postop. course uneventful.

Family 54



Family 55

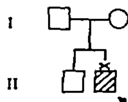


55 I.3 AK

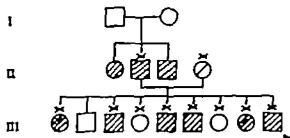
Gastro-intestinal. — At 50 and 52 years severe melaena. Roentgen examination of stomach, duodenum and colon revealed no source of bleeding. Hb on first occasion fell to 5.9 g/100 ml. The patient was given several bottles of blood. At second bleeding episode gastric resection was decided upon.

Gastrectomy — At 52 years, a few weeks after an attack of melaena, the patient was subjected to gastric resection (B.II) because of repeated gastric haemorrhage. At op. very shallow ulcer about 1 cm in diameter and at least 5 rice-seed sized superficial ulcers were found in the gastric canal. No injured artery to explain patient's severe bleeding. At op. the patient bled readily. Re-suturing was necessary both in the viscera and to the right in the abdominal wall. The day after op. the patient showed signs of intra-abdominal haemorrhage. At laparotomy there was profuse bleeding in op. field but no source of bleeding with certainty. Re-laparotomy 3 days later showed some blood in the abdominal cavity and abundant blood and clots in the stomach. Patient submitted to subtotal gastric resection and the mucosa was found to contain several superficial ulcers. The patient continued to bleed and finally *died.*

Family 56



Family 58



58 III.9 AP

Post-extraction haemorrhage — At 6 years profuse bleeding after tooth extraction. Patient admitted to hospital 1 week later with Hb 4.6 g/100 ml. Received 2 bottles of blood.

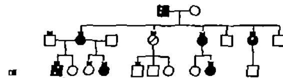
58 II 1 KF

Nose and ear — Often nose-bleeding since childhood. Cauterised several times. At 58 years left cheek hit by large branch of tree. X-ray showed small fracture in anterior wall of maxillary sinus. Profuse bleeding which ceased after a few hours. One week later severe bleeding from left nostril. Source of bleeding far back in ethmoidal area. Hb fell to 8.6 g/100 ml. — Haematotympanon bilaterally.

58 III.1 AMG

Tonsillectomy — Tonsillectomy after 6 days hospitalisation because of bleeding from tonsils at 14 years. Hb 6 days after op. 9.6 g/100 ml and 11 days after op. 6.1 g/100 ml. Bleeding ceased spontaneously.

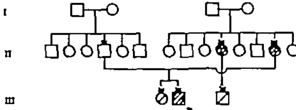
Family 59



59 III 1 TA

Tonsillectomy. — At 19 years severe bleeding on both sides after tonsillectomy. Swelling of surrounding tissue and difficulty in breathing. External carotid artery was ligated and tracheotomy was performed. Profuse bleeding also after these measures. Bleeding continued intermittently one week. Patient given 10 bottles of blood and ε-ACA.

Family 60

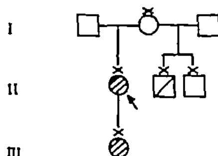


60 II.10 ES

Menstruation. — Since menarche at 14 years always copious menstrual flow. Admitted to hospital at 19 and 20 years, then had Hb 5.9 and 6.4 g/100 ml. Received blood infusions. Better after delivery at 21 years. After second delivery at 23 years symptoms again increased. Troublesome anaemia. At 31 years the patient was tired and weak owing to severe recurrent menorrhagia, and hysterectomy was decided upon (see below).

Hysterectomy. — At 31 years hysterectomy without abnormal bleeding. Patient received 2 bottles of blood. 6 days and 8 days after op. profuse vaginal bleeding. Patient received 2 bottles of blood on one occasion and 4 on the other. No bleeding since.

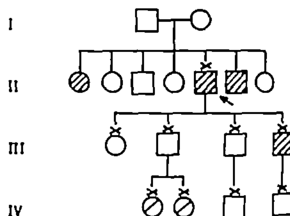
Family 61



61 II 1 ALK

Hysterectomy. — At 26 years hysterectomy because of meno- metrorrhagia. At op. the patient received 400 ml of fresh blood. Op. and the immediate postop. course were uneventful. One week after op. severe vaginal bleeding requiring tamponade and blood infusions. Tamponade was removed after a few days but about 1 week later the patient again began to bleed profusely. She received 1,600 ml blood and was again treated with tamponade. Bleeding then ceased.

Family 63



63 II.5 GL

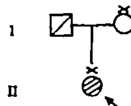
Haemoptysis. — At 85 years haemoptysis and Hb down to 7.8 g/100 ml. X-ray showed changes suggesting bronchiectasis.

Intramuscular and subcutaneous bleeding. — At 86 years pain and swelling of left thigh of unknown cause. Declive haematoma gradually developed. Hb fell to 6.6 g/100 ml. Patient treated with fresh plasma, 10x400 ml and ε-ACA. Improved.

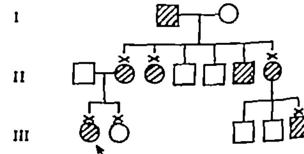
63 II:6 JL

Gastro-intestinal. — Said to have died in America from massive bleeding from duodenum.

Family 64



Family 65



65 III 1 BS

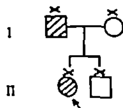
Nose-bleeding. — Frequent nose-bleeding during childhood. Electrocoagulation at least once. — At 57 years admitted to hospital because of fairly severe bleeding after blow against nose. Hb 11.1 g/100 ml.

Ear. — Had spontaneous bleeding.

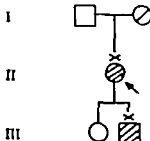
65 II.3 LR

Ablatio mammae – At 68 years operated upon be cause of breast cancer Received 1 bottle of blood at op Hospital records contained no notes about bleeding at op. Uneventful postop. course.

Family 67



Family 70

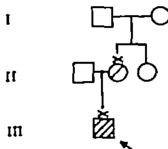


70 II.1 KH

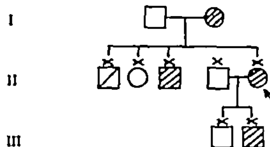
Cholecystectomy – Ay 26 years cholecystectomy + appendectomy *en passant* No notes about bleeding at op Postop. course uncomplicated except bleeding tendency in wound. Hb, however *fell from 12.9 g/100 ml* day after op. to 9.3 g/100 ml 4 days later Bleeding time (Duke) up to 12 min. Patient received 400 + 800 ml blood, but Hb one month later nevertheless was only 6.6 g/100 ml. Patient received a further 800 + 800 ml blood.

Ablatio mammae – At 26 years 2 months after cholecystectomy the patient was subjected to ablatio mammae because of nodule in left breast. Op. performed under protection of infusion of fresh plasma on op. day and within 4 days after op. all together 6x400 ml. Haematoma nevertheless developed in op. field. Hb fell from 12.7 to 9 7 g/100 ml. Patient received 2 bottles of blood.

Family 72



Family 73



73 II.5 SE

Menstruation. – Menarche at 12 years. Profuse menstruations since 14 years. Always anaemic. Hb at 34 years fell on one occasion to 6 0 g/100 ml. Patient treated several times with blood transfusions. After de livery at 27 and 32 years menstruation normal for 18 months, afterwards irregular and of same severity as be fore. Therefore treated at 38 years with hysterectomy

Hysterectomy – At 38 years hysterectomy because *of anaemising menorrhagia. Patient bled profusely* at op. and received 6 bottles of blood. On 8th – 12th day again profuse uterine bleeding. Treated with blood infusions, tamponade of vagina and then resuture of top of vagina. ε ACA, 3 g x4 given on 11th – 15th day after op. Patient improved but ε ACA withdrawn be cause of suspected pulmonary embolism. Vaginal blee ding recurred and patient continued to bleed for 14 days, and on one occasion *fell into shock*. She received abundant blood, fresh plasma and later also F I-O Repeated vaginal tamponade was done and on a further 2 occasions resuture of top of vagina. Last time ligature also round internal iliac artery After this op. bleeding *ceased* but *recurred* after 14 days, *i.e.* 43 days after the first op., but now less severe. Treated then with new ligature + suture and vaginal tamponade. Bleeding then definitively ceased. Received all together 60 bottles of blood, 30 bottles of plasma and $52^1/_2$x100 ml of F I-O

73 II.3 SJ

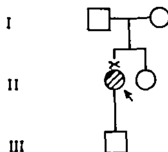
Eye-bleeding – At 34 years while shooting with an air-gun, splitter damaged left eye. 5 days later severe bleeding behind the eye Patient became almost blind on that side.

73 I.2 EJ

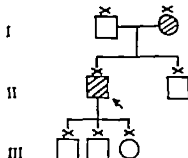
Miscarriage – At 42 years admitted to hospital be cause of Uterus myomatosus + Abortus infectiosus mens III – IV + Anaemia gravis. Uterine curettage and instrumental exaeresis. Prolonged bleeding. Hb fell to 6.1 g/100 ml. Patient received 3 bottles of blood.

Strumectomy – At 55 years operated upon because *of non toxic struma.* No abnormal bleeding at op. About 12 hours after op. the patient was *found dead* Postmortem examination revealed profuse bleeding in op. area and outside anterior part of trachea a large haematoma with two fist-sized blood clots. But these clots said not to have compressed the trachea – *No* other cause of death was demonstrable

Family 74



Family 75



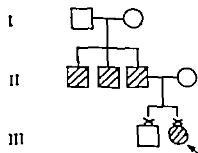
75 II 1 BT

Post-extraction haemorrhage – After tooth extractions at 21 and 26 years prolonged profuse bleeding, controlled by ligation. – Before tooth extraction at 29 years the patient received 1 bottle of blood. After extraction fairly abundant bleeding for 12 hours. Four days later bleeding recurred and the patient received a further bottle of blood. Hb afterwards 15.4 g/100 ml.

Op. intervertebral disk – At 28 years operated upon cause of herniation of intervertebral disk. Only insignificant bleeding at op. but during following days large haematoma infiltration in entire lumbar region.

Meatotomy – At 42 years operated upon because of hypospadia with meatotomy under protection of fresh plasma, 600 ml before and 3 x 400 ml within 4 days after op. No abnormal bleeding. *Eye-lid oedema and hoarseness following infusion of plasma.* Symptoms soon disappeared.

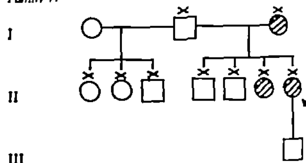
Family 76



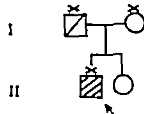
76 II.3 KGA

Gastro-intestinal – Patient *died* from gastric bleeding at 46 years. The records confirmed the cause of death but did not mention any bleeding tendency or cause of bleeding. – Two brothers are said to have *died* from haemorrhagic disease.

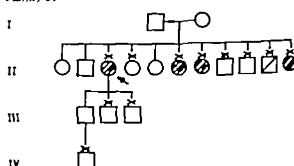
Family 77



Family 78



Family 81



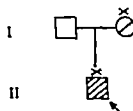
81 II.3 NF

Dacryorhinostomy – At 52 years dacryorhinostomy with severe bleeding from bed of wound but no gaping vessel demonstrable. Repeated tamponade with adrenochrom (Sangostan® Difer) and bleeding finally ceased. Hb postop. 15.0 g/100 ml.

81 II 7 ES

Cholecystectomy – At 49 years. Fairly profuse bleeding during op. from gallbladder bed. Patient received 1 bottle of blood. Smooth postop. course. Hb before op 13.1 g/100 ml, after op. + blood transfusion 15.5 g/100 ml

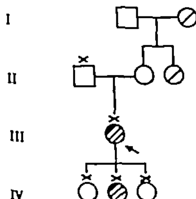
Family 82



82 II.1 AT

Urine – At 10 years repeated haematuria, particularly in association with physical exertion. Examination at hospital revealed Hb 13.1 g/100 ml and urographic examination showed nothing remarkable.

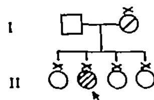
Family 86



86 III.1 AMÅ

Gastro-intestinal. – At 35 years last 10 hours before 3rd parturition, severe haematemesis. Hb fell to 7.5 g/100 ml. Vomiting of blood continued after parturition. Patient received 9 bottles of blood within 1 day. Bleeding ceased. No signs of fibrinolysis. Roentgen examination of oesophagus and stomach revealed nothing remarkable.

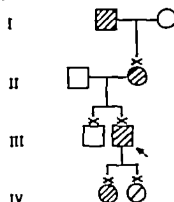
Family 88



88 II.2 IH

Hysterectomy. – At 49 years hysterectomy because of myoma. At op. no abnormal bleeding. The day after op. Hb 12.6 g/100 ml. During the following days profuse bleeding per vaginam and development of a fist sized infiltrate behind cervix. Hb 5 days after op. 7.7 g/100 ml. Patient received 1 bottle of blood and treatment was started with ε-ACA, 4.5 gx5 a day. Patient improved, but bleeding did not cease completely. 30 days after op. severe bleeding per vaginam recurred, and Hb fell to 7.4 g/100 ml. Two bottles of blood were given besides ε-ACA, 5gx4 for 14 days. But patient continued to bleed profusely for a few weeks and received a further 9 bottles of blood and 4x500 ml fresh plasma and finally 700 ml F I-O (after von Willebrand's disease had been diagnosed). The bleedings then stopped but the patient received fresh plasma also during the following 2 weeks: 5x500 ml. The patient was discharged in a good condition 11 days after the last infusion of plasma and 60 days after op.

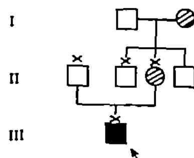
Family 89



89 III.2 HN

Hepatitis. – Treated for gastro-intestinal bleeding at 81 years with blood, fresh plasma and F I-O. Said to have had hepatitis some months later. No further information obtained, but patient recovered without complications.

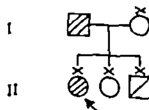
Family 90



90 III.1 ML

Bleeding after triple vaccination. – After first triple vaccination at 5 months bleeding for several hours from needle track.

Family 91



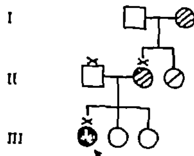
91 I 1 RS

Gastro-intestinal — Since 30 years of age gastric symptoms, worst every autumn. At 30, 31 and 35 years melaena. On 2 occasions roentgen examination showed severe catarrh but no ulcer on 1 occasion deformation of the bulb with callous changes, but no ulcer

Gastrectomy — At 35 years gastrectomy because of repeated gastric bleeding. No bleeding, however last weeks before op. Op. revealed widespread extensive perigastritis of the canal and bulb and a small callous wound in the anterior upper margin of the bulbus near the pylorus.

No abnormal bleeding at op. Eight days after op. very profuse bleeding, which continued the following day. Despite several blood transfusions the patient *died*. At autopsy the stomach was found to be distended by a very large blood clot and the small intestine and the large intestine were filled with fresh blood. The entire mucosa was dark red. No changes at site of anastomosis. The source of bleeding could not be found.

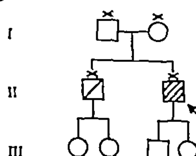
Family 92



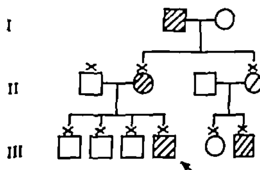
92 III 1 AM

Trauma. — Prolonged bleeding after triple vaccination and after puncture for carotis angiography. On last occasion she bled for more than one day. Given 150 ml F I-O

Family 93



Family 100



100 III 4 AS

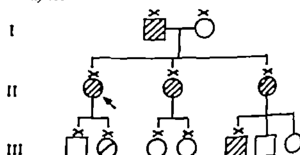
Post-extraction haemorrhage — At 3 years dental treatment at two sittings under protection of 4x100 ml F I-O each time. No abnormal bleeding. — At 6 years tooth extraction under protection of 200 ml F I-O before and 100 ml on day after op. No abnormal bleeding. About 1 week later severe bleeding from extraction cavity which was controlled by administration of a further 400 ml F I-O

100 I 1 GL

Gastro-intestinal. — At 34 years gastric bleeding. — At 61 years hospitalised under the diagnosis of duodenal ulcer with melaena. No notes about roentgen findings. Hb fell to 6.2 g/100 ml. The patient was given iron *i.v*

At 63 years haematemesis and melaena which continued for several days. Despite several blood transfusions and Macrodex the patient *died* after 5 days. At autopsy the gastric mucosa was found to be reddened and vessels just above pylorus to be dilated and the mucosa was bleeding. No ulcer. The liver was enlarged with signs of stasis and clearly cirrhotic. No oesophageal varices.

Family 101

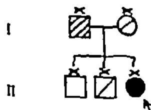


101 II 1 MO

Parturition. — Is said to have bled profusely after first 2 deliveries at 26 and 28 years. At 3rd delivery at 32 years the patient bled during the actual delivery and lost 225 ml. 4 days later profuse vaginal bleeding. Hb fell to 7.7 g/100 ml. The patient received 5 bottles of blood. Curettage produced decidua-like formation.

the size of a grape. The uterine cavity afterwards contracted and the bleeding stopped

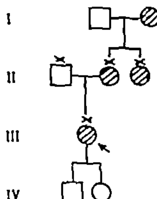
Family 103



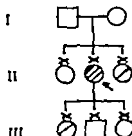
103 II.3 AW

Post-extraction haemorrhage – At 4 years extraction of milk teeth and op. because of osteitis in upper jaw. No severe bleeding at op. but troublesome bleeding during the subsequent 2 months from the op. area Hb fell to 7.9 g/100 mL. Several blood transfusions were given.

Family 105



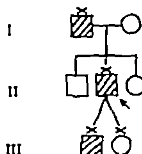
Family 107



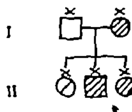
107 III.2 MB

Cholecystectomy – At 31 years cholecystectomised. Abundant bleeding both at op. and the first few days afterwards. *Hb fell to 9.5 g/100 ml. The patient received* all together 6 blood transfusions. Bleeding did not stop until after transfusion of fresh blood

Family 109



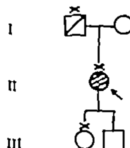
Family 111



111 II.2 T.E.

Post-extraction haemorrhage – At 5 years severe prolonged bleeding after tooth extraction. Hb fell to 6.1 g/100 mL. Three transfusions of bank-blood and 1 transfusion of fresh blood produced only transient improvement. Finally 11 days after tooth-extraction the patient was given 2x200 ml F I-O and bleeding promptly stopped. *Patient afterwards given* F I-O 100 – 200 ml a day for 10 days. No bleeding afterwards.

Family By



FREQUENCY

Improved diagnostic possibilities have resulted in a higher frequency of detection of von Willebrand's disease during the last decades. The condition has been diagnosed in various races, *e.g.* in the white race, thus also in Arabs and Jews (Salomon & Tatarski 1965) and Indians (Kasliwal et al. 1966) and in other races such as Negroes (Buchanan & Leavell 1956, Schulman et al. 1956, Arrants, Jordan & Newcomb 196., Gomperts et al. 1969) and in Japanese (Yamada et al. 1965).

In some areas von Willebrand's disease appears to be one of the commonest inherited haemorrhagic diseases with frequencies approaching those of haemophilia (Horler & Witts 1958, Achenbach 1960, Marx & Jean 1964, Horowitz & O'Leary 1965). According to Quick (1967a) and J. Jürgens (1969), von Willebrand's disease is even more common than haemophilia.

A search of the literature failed to reveal the frequency of von Willebrand's disease in any defined population.

PRESENT SERIES

The present material consisted of 658 persons belonging to 84 families. 603 persons were examined in further detail and 594 of them were still living on Jan. 1st 1968. These 594 were judged according to the criteria given on page 13 and the results are listed in Table 3.

Table 3

Occurrence of von Willebrand's disease in persons in the present material investigated with laboratory examinations and living on 1/1 1968

von Willebrand's disease demonstrated	255
Intermediate results (see page 13)	55
von Willebrand's disease not demonstrated	284
Sum	594

In January 1968 Sweden had a population of about 7.9 million inhabitants. This means that the frequency of von Willebrand's disease in Sweden was at least 255 7.9 million, 1:32,000 inhabitants.

Patients with a firm diagnosis of von Willebrand's disease were divided according to whether the disease was severe or mild, classified by the criteria on page 13. The results are given in Table 4.

Table 4

Occurrence of severe and mild von Willebrand's disease in patients in the present material investigated with laboratory examinations and living on 1/1 1968

Severe von Willebrand's disease	28
Mild von Willebrand's disease	227
Sum	255

Most of the severe cases of von Willebrand's disease had been diagnosed during the first 5 years after the disease had become more widely known in Sweden from the investigations by Nilsson et al. (Nilsson, Blombäck & von Francken 1957, Nilsson, Blombäck & Blombäck 1959). The severe cases not diagnosed within this period were all seen in children below 5 years.

The mild cases had naturally often not been examined so early and most of the mildest cases had not been discovered before the family investigations.

Summing up, there are probably only few undiagnosed severe cases of von Willebrand's disease in Sweden. It is difficult to say how many mild cases have remained undiagnosed, but the number is probably large. Many patients with mild von Willebrand's disease have not had any troublesome bleeding symptoms and the bleeding tendency has often not been discovered before provocation, such as by operation.

It might be of interest to compare the frequency of von Willebrand's disease with that of haemophilia. Ramgren (1962) found a frequency of 1:15 000 men in Sweden. Since there is a slight preponderance of females in the population the frequency for the entire population would be scarcely 1:30,000. According to the present calculation the frequency of von Willebrand's disease is at least 1:32,000. The frequency of mild cases is higher for von Willebrand's disease than for haemophilia, and the number of undiscovered cases is therefore probably higher for von Willebrand's disease. It is therefore probable that von Willebrand's disease is the commonest inherited haemorrhagic disease in our country.

The distribution of von Willebrand's disease in different districts and in Stockholm is given in table 5. The table is based on the last known addresses of the patients as well as on the origins of the affected branches of the families. The distribution according to their present

places of abode is more irregular. This is partly because certain families have a large number of affected members, most of whom are living in one district. This applies, above all, to family 42 in Kristianstad's län (L). It is also influenced by the nearness of the patients place of abode to a coagulation laboratory, which means an accumulation of cases in Stockholm (A) and Stockholms län (B), Södermanlands län (D) and Malmöhus län (M). The distribution is more even when based on the original place of abode of the affected branches of the families and then agrees fairly well with the general distribution of the population.

Table 5

Number of living patients with a firm diagnosis of von Willebrand's disease and origins of their families in various counties of Sweden and in Stockholm on Jan., 1. 1968.

Code Letter	Name	Number of inhabitants	Number of patients	Patients per 100 000 inhabitants	Origins of families: Number of families	Origins of families: Families per 100 000 inhabitants
A	Stockholms stad	767,606	30	3 9	10	1.3
B	Stockholms län	650,661	28	4.3	5	0.8
C	Uppsala län	191,868	3	1.6	2	1.0
D	Södermanlands län	243,529	16	6.6	6	2.5
E	Östergötlands län	369,847	6	1.6	4	1 1
F	Jönköpings län	299 419	1	0.3	1	0.3
G	Kronobergs län	167,328	4	2.4	1	0.6
H	Kalmar län	236,146	0	0	0	0
I	Gotlands län	53,999	0	0	0	0
K	Blekinge län	150,897	1	0.7	2	1.3
L	Kristianstads län	264,695	38	14 3	2	0.8
M	Malmöhus län	687,910	42	6.1	13	1 9
N	Hallands län	186,025	4	2.2	1	0.5
O	Göteborgs och Bohus län	684,626	21	3.1	6	0.9
P	Älvsborgs län	391,569	8	2.0	4	1.0
R	Skaraborgs län	253,863	12	4 7	3	1.2
S	Värmlands län	286,665	13	4.5	4	1 4
T	Örebro län	272,704	12	4 4	4	1.5
U	Västmanlands län	255,264	2	0 8	1	0 4
W	Kopparbergs län	281,000	2	0 7	2	0.7
X	Gävleborgs län	294,977	2	0.7	3	1.0
Y	Västernorrlands län	277,583	2	0.7	5	1.8
Z	Jämtlands län	129,275	1	0.8	1	0.8
AC	Västerbottens län	235,230	4	1 7	2	0.9
BD	Norrbottens län	260,918	1	0 4	0	0
	The whole country	7,893,704	253	3.2	82	1.0

*) 2 of the 84 probands could be traced to Finland and Germany, respectively.

INHERITANCE

Most investigators of the inheritance of von Willebrand's disease have arrived at the conclusion that the disease is autosomal dominant (von Willebrand, Jürgens & Dahlberg 1934, Matter et al. 1956, Nilsson, Blombäck & von Francken 1957, Gross & Mammen 1960, Mazzaglia & Neel 1960, Achenbach 1960, Eriksson et al. 1961, Barrow & Graham 1964, Marx & Jean 1964, Cornu 1965). Some authors, however, claim to have found families, where the disease appears to be transmitted by a recessive gene, because neither of the parents of the children affected had shown signs of the disease (Schulman et al. 1955, Verstraete 1963 and Quick 1967 a). Singer and Ramot (1956) reported that several affected children had been born in consanguineous marriages without demonstrable evidence of haemorrhagic disease in the parents. Cornu (1959) made an analysis of the literature and found that of 60 probands with a probable diagnosis of von Willebrand's disease, 4 had consanguineous parents compared with at most one expected. These findings could support the opinion, that the disease is sometimes inherited recessively.

The frequency of demonstrated heredity varies from one report to another. Relatively few investigators have any personal series of several families, and the frequencies reported are usually based on compilations from the literature. Here it should be borne in mind that cases with known heredity are more likely to be published than cases without. On analysis of the literature on "Maladie de Willebrand" Revol, Favre-Gilly and Oflagnier (1950) found 82 probands. Heredity was clearly demonstrable in 57 cases, doubtful in 5 and not demonstrable in 20. Cornu (1965) reported typical heredity in 20 / of the cases of von Willebrand's disease but AHF-deficiency in one or more of the direct ascendants of 80 of the patients. Sherlock (1964) and Strauss and Bloom (1965) stressed the frequent occurrence of sporadic cases.

The penetrance and expressivity of von Willebrand's disease has often been reported to vary widely (von Willebrand 1931, Matter et al. 1956, Lehmann 1959, Achenbach 1960, Eriksson et al. 1961, Strauss & Bloom 1965 and Larrieu et al. 1968). Several investigators have found, that the disease was more common among females than among males (von Willebrand 1926, Soulier & Larrieu 1954, Singer & Ramot 1956, Nilsson, Blombäck & von Francken 1957 and Valberg & Brown 1958) and that the clinical picture was often more severe in the females (von Willebrand 1926, Matter et al. 1956).

Graham (1959) suggested the possibility that different changes of importance for the bleeding tendency in von Willebrand's disease may be inherited separately and then often one from the father and the other from the mother. He supported this theory partly on one of the first papers published by Nilsson et al. (Nilsson, Blombäck & von Francken 1957) on Swedish patients with von Willebrand's disease. Thus, in some of the families the mother or her relatives had a low AHF while the father or his relatives had a prolonged bleeding time. Also other authors (Verstraete 1963, Barrow & Graham 1964, Bowie et al. 1967) have stressed that in family investigations they found reduced AHF content and normal bleeding time in one member and a normal AHF but a prolonged bleeding time in another.

PRESENT SERIES

Mode of Inheritance

In the present investigation parents, siblings and children of most of the probands were examined. In the large family 42 an autosomal dominant mode of inheritance was illustratively demonstrable. In a further 22 families the disease had been demonstrated in three consecutive generations.

In 40 families both parents of probands were examined for AHF and regarding bleeding time and often also platelet adhesiveness by the method of Salzman. The occurrence of von Willebrand's disease in the parents of these 40 probands is shown in Table 6.

Table 6

Occurrence of von Willebrand's disease in parents of 40 probands whose father and mother had both been examined

One parent	Other parent	Number of families
+	Int.	2
+	–	27
Int.	–	7
–	–	4

+ = von Willebrand's disease demonstrable
Int. = intermediate results (definition on page 13)
– = von Willebrand's disease not demonstrable

27 families thus presented the expected pattern in autosomal dominant inheritance with one parent clearly affected and the other clearly unaffected.

Of certain interest are the two families (58 and 103), where one of the parents was affected, while the results for the other were regarded as intermediate. In those two families the father was a bleeder but the mother also had signs of the disease. The proband in family 103 (II.3 AW) had the severe form of the disease, and it does not appear unreasonable to suppose that she was homozygous in respect of the gene for the haemorrhagic diathesis. In family 58, however the proband (III:9 AP) had the mild form of the disease, and it appears less likely that he should have inherited the disease from both parents.

Investigation of the parents lent further support to the opinion that von Willebrand's disease is transmitted dominantly yet with incomplete penetrance. It appears less likely that the disease is transmitted alternately by a dominant and a recessive gene. But three of our probands have consanguineous parents (fam. 12, fam. 17 and fam. 25). The proband in family 12 has the severe form of the disease.

Frequency of demonstrated heredity

Frequency of demonstrated heredity for the probands in the present material is apparent from Table 7

Table 7

Frequency of demonstrated heredity in the probands

	Number of probands
von Willebrand's disease demonstrated in one of the parents	36
Disease not found with certainty in parents but in other close relatives	15
Clear anamnestic bleeding tendency in parents or close relatives, not available for lab. invest.	8
Sum	59
Signs of the disease in parents or close relatives but disease not demonstrated with certainty	15
No anamnestic or clinical signs of the disease in the family	10

In those cases with no signs of heredity examination of members of the family was usually very limited because the close relatives of the proband were either dead or otherwise not available for examination

Penetrance and expressivity

Great variation as to penetrance and expressivity was seen in the present material

The percentage for penetrance was calculated from the investigation of parents of 40 probands (Table 6) At least one of the parents was found to be affected in 29 of the 40 families. In a further 7 families intermediate results were obtained for one of the parents. This means a penetrance of at least 73 and of at most 90 %. Examination of 52 children of probands has given the results seen in Table 8

Table 8

Occurrence of von Willebrand's disease in 52 investigated children of probands

	Number of children
von Willebrand's disease demonstrated	15
Intermediate results	4
von Willebrand's disease not demonstrated	33

These figures suggest a somewhat lower penetrance: at least 58 and at most 73 %

The expressivity of the disease varied considerably also within one and the same family. Such was the case, for example, in family 2 with low expressivity in the sibship II.4 – II 18 but much higher in the sisters III.2 and III 3

In our patients, however the expressivity within the sibships was more uniform than in non-relatives, as shown by statistical test for AHF the results of which are given in Table 9

Table 9

Analysis of variance of AHF

Variation	df	msq
between sibships	41	322
within sibships	80	87

df degrees of freedom msq mean square
F 3 7 i.e. $p < 0.001$

Large differences in expressivity between members of the same sibship were rare in the present material. Patients with the severe form of the disease had investigated siblings with the severe form in three cases (families 2, 4 and 13). On the other hand only one patient with

the severe form of the disease had a sibling with the mild form (fam 23)

The AHF-dependence of affected children on affected parents was examined with the X^2-test. It was found that the resemblance between these parents and their children was closer than between the same parents and unrelated children. The resemblance seemed less striking than that found for siblings, but the test showed that the dependence was significant: $X^2 = 6.22$, df = 1 $p < 0.05$

Expressivity in males and females

The sex distribution of the present material is given in Table 10

Table 10

Sex distribution in the Swedish von Willebrand series

	Males	Females
Probands	34	50
Others with diagnosed von Willebrand's disease	76	104
Total	110	154
Of which severely ill	9	23

Of the probands, 22 were examined concerning their bleeding time and coagulation factors because of bleeding from the female genital tract. This might explain the preponderance of females among them. But females were also more common among other patients. Here, too, however bleeding from the genital tract may explain why they were more often classified as bleeders. It is remarkable, however that the frequency of the severe form of the disease was more than twice as high among females as among males. Here, the severity of the disease was based mainly on laboratory values. The difference between the sexes in these cases can hardly be ascribed to the fact that the bleeding tendency more readily produced symptoms in females The figures were, however small and the difference was not statistically significant.

Are prolonged bleeding time and low AHF inherited separately?

In the present material there were three families (Nos 4 13 and 23), in which the AHF-content appeared to be abnormal in one of the parents and the bleeding time in the other But in one case (4 III.1 DD) with prolonged bleeding time at the first examination a normal value was obtained at control. In the other two families the values for one of the parents (13 II 10 AE and 23 II 15 GW) are uncertain and unfortunately could not be checked. In some families we found sibships (29 III 2 ÅW and III:4 ÅH, 42 IV.35 RN and IV.38 MN 59 II:2 SA and II 7 GÖ) in which one of the members had only a reduced AHF-content and another only a prolonged bleeding time. Closer analysis of these patients showed, that nearly all of them had a very mild form of the disease or that the diagnosis of the disease was doubtful. In most cases the lack of correlation between disturbance of AHF-content and of bleeding time can be ascribed to errors of the methods used. These errors make themselves felt especially in patients with values lying close to the limits of the normal ranges.

Table 11

Correlation between AHF and bleeding time

Bleeding time by the method of	AHF / 0–20	21–40	41–64	≥65
Duke >30′	25	7	2	
Duke <30′ Ivy >30′	3	27	29	10
Ivy 16–30′	2	25	59	53
Ivy ≤15′ [1]		5	46	167

[1] In Stockholm ≤12′

Table 11 of the relationship between AHF and bleeding times, which comprises most of the persons examined, both healthy and affected, is here of interest. It shows largely good agreement between reduced AHF and prolonged bleeding time. This concordance is convincing particularly in the severe form of the disease. Patients with a Duke bleeding time of less than 30 minutes but no determinations of the Ivy bleeding time could not be fitted into the table.

SYMPTOMATOLOGY

CONTROLS

For evaluating anamnestic haemorrhagic symptoms in suspected von Willebrand's disease, histories were taken of a number of persons without known bleeding disease or heredity.

The control series consisted of children above two years and seen at the outpatient unit of the department of pediatrics, Kristianstad central hospital, and the parents or other relatives, who had brought the children to the hospital. The series consisted of 500 persons (63 males and 210 females above 15 years and 227 children below 15 years). The series is not ideal, but was considered acceptable for assessing the frequency of certain common haemorrhagic symptoms. Parous women were overrepresented in the group of females. Only few of the adults were above 50 years, and this may have influenced the frequency of above all, gastro-intestinal and certain postoperative haemorrhage.

The results of examination of the control series are given in Table 12.

Table 12

Frequency (%) of various sorts of bleedings among 500 persons without known haemorrhagic disease.

	+	+ +		Sum.
Nose bleeding	2.2	[illegible].4		4.6
Gingival bleeding	7 2	0.2		7 4
Traumatic oral and lip bleeding	0 6			0.6
Gastro-intestinal bleeding	0 2	0.2	0.[illegible]	0.6
Haematuria		0 6		
Meno-metrorrhagia	16.7[1])	8.6[1])		25.3[1])
Bleeding at delivery	9 0[1])	5 7[1])	4.8[1])	19.5[1])
Ecchymoses and haematoma	11.8[2])			11.8[2])
Petechiae	0.8	0 4		1.2
Bleeding from trivial sores and wounds	0.2			0.2
Joint bleeding				
Post-extraction haemorrhage	3 6	1 2		4 8
Postoperative bleeding		0.8	0.6	1 4

\+ = bleeding often or profuse
\+ + = bleeding requiring medical, surgical or dental treatment
\+ + + = bleeding requiring blood transfusions
[1]) Calculated for females above 15 years
[2]) Bleeding often or profuse in the form of ecchymoses and haematomas occurred in females above 15 years with a frequency of 20.5 %.

FREQUENCY OF HAEMORRHAGIC SYMPTOMS IN VON WILLEBRAND'S DISEASE

The frequency of various haemorrhagic symptoms in the present series of von Willebrand's disease is given in Table 13. Types of bleeding occurring in only three patients or less have not been included (see page 99).

For comparison the table includes the figures obtained by Buchanan and Leavell (1956) in a survey of the literature on "pseudohemophilia". No such compilation has been published since, and it appears, that no calculation has been made of haemorrhagic symptoms in a large series of patients with a firm diagnosis of von Willebrand's disease. Broadly speaking, the frequencies in our series agree relatively well with the data given by Buchanan and Leavell.

The table also includes figures for the control series, which shows a high frequency of, above all, meno-metrorrhagia, post-partum haemorrhage and cuts

Table 13
Frequency (%) of remarkable bleeding[1]) in the Swedish series of von Willebrand's disease, in Buchanan and Leavell's series and in a series of persons without known haemorrhagic disease.

	Swedish series 264[2]) cases	Buchanan & Leavell Men 95 cases	Buchanan & Leavell Women 104 cases	Normal material 500 cases
Nose bleeding	62.5	73	64.5	4.6
Meno-metrorrhagia	60.1[3])		51	25.3[3])
Post-extraction haemorrhage	51.5	28.5	36.5	4.8
Ecchymoses and haematomes	49.2			11.8
Ecchymoses		55.7	67	
Haematoma		8.5	7.5	
Bleeding from trivial sores and wounds	36.0	37	33.5	0.2
Gingival bleeding	34.8	33	36	7.4
Postoperative bleeding	28.0	19	20	1.4
Bleeding at delivery	23.3[3])		10.5	19.5[3])
Gastro-intestinal bleeding	14.0	24.5	9	0.6
Traumatic oral and lip bleeding	11.7			0.6
Petechiae	11.5	16	18.5	1.2
Joint bleeding	8.3	12.5	5	0
Haematuria	6.8	7.5	2	0.6
Other genital bleedings		1	7.5	
Ovarian bleeding	6.8[3])			
Bleeding from tonsils	6.1			
Bleeding during shedding of teeth	4.9			
Bleeding at abortion	3.8			
Intramuscular deep subcutaneous or submucous bleeding	2.7			
Bleeding from ears	3.0			
Haemoptysis	1.9			
Bleeding during eruption of teeth	1.5			

[1]) Types of bleeding occurring in 3 patients or less not included
[2]) Patients with a firm diagnosis of von Willebrand's disease
[3]) Calculated for females above 15 years

neous bleeding. It is remarkable that heavy bleeding at delivery was almost equally common among normal woman (above 15 years) as among woman with von Willebrand's disease. This may be explained largely by differences in parity between the two groups and is discussed further on page 96.

The findings in the controls showed that caution should be exercised in the evaluation of meno-metrorrhagia, loss of blood at delivery and cutaneous bleedings.

It is also clear from the table that the commonest haemorrhagic symptoms in von Willebrand's disease are nose-bleeding, cutaneous bleeding, bleeding from the female genital tract, and profuse bleeding after tooth extraction.

The frequency in Swedish patients of different bleeding symptoms, which required blood transfusions or proved fatal are given in a separate Table (14). The cases are classified as severe or mild according to the definitions on page 13. Most of the serious haemorrhages occurred in patients with the severe form of the disease, although they constituted only a minor part of the entire material. In the patients with mild von Willebrand's disease, severe bleeding was commonest in the form of postoperative haemorrhage, meno-metrorrhagia, gastro-intestinal bleeding and post partum haemorrhage.

Table 14

Occurrence of bleeding requiring blood-transfusion or resulting in death among Swedish patients with a firm diagnosis of von Willebrand's disease.

	Type of von Willebrand's disease		
	Severe 32 patients	Mild 232 patients	Total
Postoperative bleeding	7	27	34
Meno-metrorrhagia	12	15	27
Gastro-intestinal bleeding	8	18	26
Nose-bleeding	17	5	22
Post-extraction haemorrhage	10	7	17
Bleeding at delivery	3	10	13
Traumatic oral or lip bleeding	8	1	9
Gingival bleeding	7		7
Bleeding from tonsils	7		7
Bleeding from trivial sores and wounds	5		5
Bleeding during shedding of teeth	4		4
Ovarian bleeding	5		5
Joint bleeding	2	1	3
Intracranial bleeding	2		2
Bleeding during eruption of teeth	1		1
Total	98	84	182

BLEEDING FROM DIFFERENT ORGANS

In the following description of the clinical picture bleeding from different organs will be discussed in detail.

Nose-bleeding

Nose-bleeding is thus the commonest symptom of von Willebrand' disease and occurs with a frequency of 70–80 % (Estren, Medal & Dameshek 1946, Levy 1947 Macfarlane & Simpkiss 1954 Nevanlinna, Ikkala & Vuopio 1962 and Cornu 1965). The symptom is commonest during childhood and adolescence (von Willebrand 1933a, Waller & Gross 1964 and Bowie et al. 1967).

Nose-bleeding may occur spontaneously but some stimulating or provoking factor is often detectable von Willebrand found his patients to have nose-bleeding fairly often if they worked in a bent posture during the warm season of the year According to Achenbach (1960), nose-bleeding is apt to occur in patients with von Willebrand's disease, particularly after consumption of coffee and/or alcoholic beverages as well as after physical exertion, particularly in summer Achenbach also pointed out that nose-bleeding often occurs after surgical operation on any part of the body Trauma as a cause of severe nose-bleeding has been reported by for example, McCammon (1967).

Nose-bleeding may sometimes be very profuse and occasionally even fatal in patients with von Willebrand's disease (von Willebrand, Jürgens & Dahlberg 1934 Hewlett & Haden 1948, Dartt 1955 and J Jürgens 1959)

Present series

Of the present patients 165 (62.5 %) reported trouble some or recurrent nose-bleeding, 84 had sought medical advice for such bleeding The haemorrhage had occurred most often during childhood and adolescence and had then been more severe than in later life (Fig. 4, page 105)

Profuse nose-bleeding had often occurred in our patients in association with some other bleeding manifestation, such as bleeding from the tonsils (26 III.2 EF), bleeding after rupture of the hymen (3 III.1 MH) and bleeding after miscarriage (42 II.2 GÅ).

As in Achenbach's compilation, fairly severe nose-bleeding often occurred in our patients after surgery such as tooth extraction (42 III.21 SN III.25 SN and III.26 EN), operation because of mastoiditis (13 III.2 SE), operation because of ovarian cyst (? III.2 YL) and hysterectomy (16 III 1 AKZ)

Many of the patients reported bleeding, sometimes fairly severe, after a blow against the nose (24 III 1 RA, 26 III.2 EF 58 III.2 KF and 65 III.1 BS).

One woman (22 II 1 ID) had severe nose-bleeding on interruption of long term treatment with "p-pills" because of menorrhagia.

In 22 patients nose-bleeding had required blood transfusions. 17 of these patients had von Willebrand's disease of the severe type according to the definition on page 13

Two children had died from nose-bleeding, a girl aged 6 years (4 IV.2 AB) and a boy aged 8 years (30 III 1 ÅW). In neither had von Willebrand's disease been diagnosed, but both were siblings of children in whom von Willebrand's disease was later diagnosed.

Gingival bleeding

In the medical literature on von Willebrand's disease it is practically only von Willebrand himself, who has devoted serious attention to gingival bleedings (von Willebrand & Jürgens 1933:a). According to him, gingival bleeding is more common in this disease than in any other haemorrhagic diathesis except scorbutus. The gingival tissue is often flabby and inflamed. Several of his patients had long episodes of almost continuous gingival bleeding, interfering with the intake of food and sometimes disturbing their sleep.

Gingival bleeding is common during tooth-brushing also in the population in general, especially in persons with gingivitis or paradentosis. Thus gingival bleeding on some occasion or another was often reported by our controls. 7.2 of them had had frequent or profuse gingival bleeding during tooth-brushing, but only one of 500 had sought medical advice because of such bleeding.

Present series

Substantial gingival bleeding was reported by 92 patients (34.8). In many of them bleedings had occurred only during tooth-brushing. Others said that they had also occasionally bled spontaneously. Sometimes they had bled during the night and awakened in the morning to find blood on the pillow

In the present series remarkable gingival bleeding was most common among children and young women. In the children it often occurred in association with eruption or shedding of the teeth. It was rarely serious, but 8 had bled so profusely as to require blood transfusions. In several of these cases there were contributory causes of the severe bleeding, namely eruption of tooth (8 II 1 RB), removal of tartar (33 III.2 AR) and periodontal ostitis with fistulation (103 II.3 AW). Two patients had simultaneous severe nose-bleeding (1 V.5 BT and 4 IV.2 AB).

Bleeding during eruption and shedding of teeth

In 1931 von Willebrand pointed out that physiological shedding of the teeth can cause bleeding in von Willebrand's disease. Such profuse bleeding in association with shedding of teeth has since been described by *e.g.* Raccuglia and Neel (1960), Bonechi and Pasero (1964) and Henrion and Cornu (1964).

Present series

Four of our patients reported bleeding during eruption of teeth (7 III.1 MA, 8 II.1 RB, 40 III.3 AMW and 64 II 1 GJ). One of these (8 II 1 RB) had profuse bleeding from surrounding gingiva, which required blood transfusion.

Bleeding in association with shedding of teeth had been noted in 12 patients, including 9 with severe von Willebrand's disease. Ten children, aged 5 – 12 years, had sought medical or dental advice because of such bleeding. Four of them (7 III 1 MA, 16 III.1 AKZ, 40 III.3 AMW and 103 II.3 AW) had received blood transfusions to replace the blood loss.

Traumatic oral bleeding

In von Willebrand's disease traumatic bleeding from the lips and oral cavity is fairly common in the first years of life. A search of the literature revealed 25 cases of such bleeding including 22 in children of at most 3 years of age. The bleeding often made blood transfusions necessary and was fatal in two cases, published by von Willebrand (1926) and by Gomperts et al. (1969).

Present series

Such bleeding had occurred in 31 of our cases, including 21 in which the disease was severe. The bleedings had occurred mostly in small children (see Fig. 4 page 105), who had fallen and hit themselves and sustained a small injury of a lip, of a frenulum or of the

tongue. The wounds in the tongue had then generally been caused by biting.

In 23 cases medical advice had been sought, often because the bleeding had continued for several days with substantial loss of blood and a fall of the Hb to 5–9 g/100 ml. Many of the children had been repeatedly admitted to hospital because of such bleeding. In 9 cases the haemorrhage had necessitated blood transfusions.

Tonsillar bleeding

Tonsillar bleeding has been described in only a few cases of von Willebrand's disease (Ascari, Barbieri & Gobbi 1964, Wake & McClure 1965, Lemoyne & Larrieu 1967 and J. Jürgens 1969).

Present series

Spontaneous tonsillar bleeding had occurred in 16 of our cases, including 10 with the severe form of the disease. The haemorrhage had usually occurred in association with tonsillitis. In 13 cases medical advice had been sought and in 7 blood transfusions had been given.

One patient (23 III.2 KW) had had such frequently recurrent and severe tonsillar bleeding that she had finally been subjected to tonsillectomy. The operation had been performed under protection of Fraction I-O without any complications.

Ear bleeding

Present series

Verified or probable ear bleeding had occurred in 8 of our patients. In 6 of them the haemorrhage had occurred during childhood. In 3 of them analysis of blood samples had suggested the severe type of the disease.

Three of the patients had haematotympanum, in one of them (20 III.2 KGP) with simultaneous nose bleeding and in another (58 II 2 KF) after trauma. One boy (13 III.2 SE) had had a Hb of 5.6 g/100 ml during otitis, which had aroused the suspicion of ear-bleeding. One girl (40 III.3 AMW), was deaf on one side and the deafness was thought to be due to adhesions in the middle ear as consequence of bleeding. Three patients (7 III.1 MA, 17 IV 1 EL and 65 III 1 BS) had had spontaneous bleeding from the ears.

Pulmonary haemorrhage

Haemoptysis is said to be uncommon in von Willebrand's disease. It is possible that it had occurred more often before von Willebrand's disease had become widely known, and when tuberculosis was a much more common disease than it has been during the last decades. Koch et al. (1957) mentioned a case of pulmonary tuberculosis with severe bleeding. Marx and Jean (1964) described a boy who had von Willebrand's disease and whose three paternal uncles had apparently died from haemoptysis. W. Perkins (1946) reported a patient with von Willebrand's disease whose paternal great-grandfather had shown signs of a bleeding tendency and who had died at 56 years from sudden pulmonary haemorrhage. A more recent case of severe haemoptysis and concomitant haemothorax of unknown origin was reported by Bowes (1969).

Present series

Five of our patients investigated had had haemoptysis. Two others had presumably died from pulmonary haemorrhage. These two were the paternal grandmother and the paternal aunt of 17 IV:5 LL, and at least the paternal grandmother was said to have had other signs of bleeding tendency, particularly nose-bleeding. Both patients had died before the investigation had been started.

Two of our other cases with haemoptysis (38 III 7 EP and 42 III.20 BN) had verified pulmonary tuberculosis.

An old man (63 II 5 OL) had massive pulmonary haemorrhage at 85 years and a Hb down to 7.8 g/100 ml. Roentgen examination showed pulmonary changes compatible with bronchiectasis.

A further two patients (11 II.1 GB and 91 II 1 MS) had had haemoptysis, but the source of bleeding had not been demonstrated. In neither of these two cases had the loss of blood been heavy.

Ecchymoses and haematoma

Cutaneous haemorrhage, mostly in the form of ecchymoses and haematoma, is a characteristic symptom of von Willebrand's disease. Ready bruisability is common; Imershand (1949) and Corrin (1965) give as high a frequency as 100 %. This frequency must, however, be evaluated with caution, such bruisability being common also in persons without haemorrhagic disease. In the present control series it was reported by as many as 20.5 % of the females above 15 years.

Present series

130 patients in the present series (49.2 %) reported that they bruised very readily. 13, including 9 with the severe form of von Willebrand's disease, had sought medical advice because of severe or numerous haematomas.

In many of our patients ready bruisability was the symptom that had first drawn attention to the increased bleeding tendency.

Petechiae

Petechiae are less common in von Willebrand's disease (Buchanan & Leavell 1956, Matter et al. 1956, Biggs & Macfarlane 1957, Achenbach 1960, Raccuglia & Neel 1960, Cornu 1965, Horowitz & O'Leary 1965).

Present series

30 (11.5 %) of our patients with von Willebrand's disease had had the symptom on some occasion. In 17 of the 30 patients the AHF was very low (less than 20 %) and in 14 the bleeding time by the method of Duke was very long (more than 30 minutes).

Intramuscular, subcutaneous and submucous haemorrhages

In contrast with what is seen in haemophilia, large soft tissue haematomas are uncommon.

In those relatively few cases where the symptom has been described the AHF values were low: between 2 and 20 % (Biggs & Macfarlane 1957, Raccuglia & Neel 1960, Ascari, Barbieri & Gobbi 1964, Lewis 1964, Wake & McClure 1965, Ponka, Monto & Welborn 1967) though not so low as in severe haemophilia. The bleeding time by the method of Duke was only moderately prolonged, 7 minutes – 28 minutes.

Present series

Only 8 patients in the present series had had known intramuscular or large subcutaneous or submucous haemorrhages.

Most impressive was the bleeding in the floor of the mouth in 16 III 1 AKZ following life-threatening menorrhagia, which had required several blood transfusions. The bleeding occurred around a carious tooth and spread in the floor of the mouth and threatened to obstruct the larynx.

One patient (6 IV.2 RF) had a large inguinal haematoma with stasis in the entire leg after puncture of the femoral vein. 13 III.2 SE had had intramuscular bleeding in the calf when he had been run into by an autocycle. These were the only patients in whom intramuscular bleeding had been caused by known external trauma.

Seven patients who had had large soft tissue haematomas also had very low mean AHF values (less than 10 %). This suggests that the mechanism underlying the bleeding may have been similar to that in haemophilia. Also the bleeding time by the method of Duke had, however, been very prolonged (more than 30 minutes).

Traumatic haemorrhage

Bleeding from trivial wounds and injuries and after puncture

Prolonged bleeding from small wounds was described as characteristic of the disease already by von Willebrand (1933:a). He described such bleeding as more severe than in thrombocytopenia. This type of bleeding is also to be expected in a disease in which a prolonged bleeding time is one of the most important examination findings. The frequencies vary from one series to another up to 100 % (Levy 1947, Imershund 1949). It is difficult to assess the severity of the symptom because the evaluation is usually based only on the patient's reports.

Present series

95 of the Swedish patients reported prolonged bleeding from trivial wounds and injuries. In only 8 cases was medical treatment required. In 5 patients (2 III.2 YL, 4 IV.1 GB, 6 IV.2 RF, 33 III.2 AR and 48 III.1 BH), all with the severe form of von Willebrand's disease, the loss of blood was so massive as to make blood transfusions necessary.

In some of our patients severe or prolonged bleeding occurred after puncture for injection (4 IV 1 GB, 90 III 1 ML, 92 III 1 AM) or for sampling (6 IV.2 RF, 33 III.2 AR and 92 III.1 AM). In a couple of these patients (4 IV 1 GB and 6 IV.2 RF) the bleeding assumed the form of a large haematoma or soft tissue haemorrhage, while in others it was a question of prolonged oozing external bleeding. Two of the patients received blood transfusions because of the blood loss (4 IV 1 GB and 33 II.2 AR).

Bleeding after severe trauma

Remarkable bleeding after severe trauma is rare in von Willebrand's disease. A few cases of relevant

Table 15
Cases from the literature with profuse bleeding after trauma

Author	Patient	Injury	Haemorrhage
Klesper & Achenbach 1957	Female 9 years	Rammed	Life-threatening
Kyle & Baker 1964	Male, 17 years	Complicated lower leg fracture with local haematoma and haematoma in knee	Pat. received 5 liters of blood
Marx & Jean 1964	Male	Fall from 7 m height	Pat. given blood-transfusions
W. Perkins 1946	Male	Skull fracture	Died from bleeding
Wake & Mc Clure 1965	Male	Fall on forehead	Haematoma that spread. Pat. given blood transfusions

interest published are given in Table 15 (Intracranial bleeding owing to trauma is discussed in the chapter on intracranial haemorrhage below).

The injuries, at least in those cases described by Klesper and Achenbach and by Marx and Jean, were so severe that they might have caused a heavy loss of blood also in persons without any bleeding tendency.

Present series

In Swedish patients severe trauma (apart from skull trauma, see below) caused massive bleeding most often, when the accident had injured serous membranes or mucosae. Thus, joint bleeding was observed in some cases after knee injury (see page 99), nose-bleeding after jaw and face injuries (page 88), and pleural bleeding after trauma of the thoracic cage (page 100).

Severe trauma had otherwise not caused any remarkable bleeding in our patients. Judging from the patients reports and notes in their hospital records, fractures had not caused serious bleeding complications. Only in two cases (6 IV.2 RF and 13 III.2 SE) had known trauma caused intramuscular bleeding.

Bodily injuries had sometimes caused large superficial haematomas but not any fall in the blood values. Large external bleedings had occurred only in those cases described under the heading of bleeding from trivial wounds (page 90).

Intracranial haemorrhage

Intracranial haemorrhage is uncommon in von Willebrand's disease (Estren, Medal & Dameshek 1946, Lelong & Soulier 1950, Buchanan & Leavell 1956, Nevanlinna, Ikkala & Vuopio 1962 and Cornu 1965).

Spontaneous meningeal bleedings with favourable outcome have been reported by Cornu et al. (1961) and J. Jürgens (1969). The latter had seen no less than 4 cases, and all of them had had arterial aneurysms.

Schulman et al. (1956) described a case of intracranial bleeding at birth with mild residual hemiparesis. Minot (1928) published data on a 5 year old boy in whom skull trauma was followed by an extradural haematoma that was successfully evacuated under protection of two blood transfusions.

Kaliwal et al. (1957) and Koch et al. (1957) reported one case each with fatal intracranial haemorrhage, which seems to have occurred finally after severe bleeding from other organs.

Horowitz and O'Leary (1965) and Meili, Straub and Frick (1969) briefly mentioned two cases and one case, respectively of fatal intracranial haemorrhage in relatives of patients with von Willebrand's disease. One of these patients (Meili, Straub & Frick 1969) had a skull injury after fall from a bicycle.

Of the above 12 cases, 5 were fatal. Only one of those 5 patients had a history of trauma.

Present series

Intracranial bleeding occurred in three of our patients in whom von Willebrand's disease had been firmly diagnosed. All three had the severe form of von Willebrand's disease, the bleeding time had been very long and the AHF-values very low (Table 16).

After a fall from a height of $2^1/_2$ meters 7 III 1 MA had had a subdural haematoma, which had been successfully evacuated. Roentgen examination had shown no fracture. After the operation there was profuse bleeding, which was, however controlled by blood transfusions.

Table 16
Cases of intracranial bleeding in Swedish patients with a firm diagnosis of von Willebrand's disease

Patient	Age years	Bleeding time by method of Duke	AHF %	Trauma
4 IV 1 G.B.	24	>30'	4.7	Mild blow with flat hand
7 III 1 M.A.	3	>30'	4.5	Fall from slide
13 III.3 J.I.E.	14	>30'	3.5	Fell from cycle and hit head

The other two patients had sustained only mild or moderate trauma, which had, however proved fatal after one and eight days, respectively. In neither could any fracture be demonstrated. In one of the patients (4 IV 1 GB) there was a haematoma under the left temporal bone, in the other (13 III.3 JIE) a haematoma, the size of a hen's egg, in the right frontal lobe and small subdural haemorrhages. Neither of the patients had received any effective treatment to stop the bleeding.

In these two cases, then, relatively mild trauma had thus been fatal as it is sometimes seen in haemophilia (Ramgren 1962, Kerr 1964, Biggs & Macfarlane 1966, Blattner 1967).

A further Swedish patient who probably had von Willebrand's disease (49 II.3 AA) had died, presumably from intracranial bleeding that had occurred "fall from a moderate height". He had never been regarding his bleeding and coagulation sta , but he had previously had massive bleeding also from the stomach and the urinary tract. Two daughters had verified von Willebrand's disease. Autopsy was not done.

Gastro-intestinal haemorrhage

Gastro-intestinal bleeding was not common in the Åland family described by von Willebrand, but when it occurred it was frequently serious (von Willebrand 1926 and 1931, von Willebrand & Jürgens 1933:a, von Willebrand, Jürgens & Dahlberg 1934). Eriksson (1962) examined the family for bleeding from the upper gastro-intestinal tract. He found that in the last 6 generations 14 persons had died from spontaneous bleeding and in 8 of these gastro-intestinal bleeding had been the cause of death.

In most published series the frequency of gastro-intestinal bleeding is low (Estren, Medal & Dameshek 1946, Levy 1947, Imerslund 1949, Macfarlane & Simpkiss 1954, Sherlock 1964, Horowitz & O'Leary 1965, Strauss & Bloom 1965 and Wake & Mc Clure 1965), as a rule about 10 %. In their compilation of 1956 Buchanan and Leavell found a somewhat higher figure (16.5 %) as well as a higher frequency for males than for females.

When gastro-intestinal bleeding occurred, it was usually severe. Such bleeding was sometimes long and disabling and often recurrent and life-threatening (Brandstetter et al. 1966, Marx & Jean 1964, H. Perkins 1967, Stroehlein et al. 1968). Fatal haematemesis and melaena have also been reported (von Willebrand 1926 and 1931, Achenbach et al. 1959, Carré et al. 1961, Eriksson 1962, Bonechi & Pasero 1964 and Brandstetter et al. 1966).

The source of bleeding from the gastro-intestinal tract is often difficult to locate. The results of roentgen examination have often proved negative or uncertain (Weiss 1962, Salomon & Tatarski 1965, Brandstetter et al. 1966, H. Perkins 1967). Clear-cut ulcer has rarely been detected (Eriksson 1962, Laget-Corsin & Parquet-Gernez 1968). In some cases examination has revealed deformation of the duodenal bulb, suggesting previous ulcer but not an actual crater (Eriksson 1962, Ponka, Monto & Welborn 1967, Stroehlein et al. 1968). In one case diverticuli of the colon have been found as a possible cause of intestinal bleeding (Marx & Jean 1964). In another case (Kyle & Baker 1964) laparatomy revealed bleeding longitudinal ulcerations in the cardia, so-called Mallory-Weiss syndrome.

Closer examination of the gastric mucosa revealed superficial ulcerations that had not been demonstrable in the roentgenogram of one patient who had died

(Brandstetter et al. 1966) and in one operated upon (Pooka, Mouto & Welborn 1967).

In patients with gastro-intestinal bleeding but without any known bleeding disorder a clear source of bleeding is much more commonly found. Schiller Trulove and Williams (1970) made an analysis of a large series of such haemorrhages in all together 2.149 patients at Radcliffe Infirmary in England. A source of bleeding could be traced in 73.8 of these cases.

Severe gastro-intestinal bleeding has sometimes occurred in children, e.g. in the Åland family (Eriksson 1962). As a rule, however it has occurred in adults, often between 40 and 60 years, when the bleeding tendency in von Willebrand's disease is otherwise less severe

Present series

Gastro-intestinal bleeding had occurred in 37 Swedish patients with von Willebrand's disease, diagnosed at coagulation laboratories. Furthermore, 10 relatives with anamnestic bleeding tendency had had bleedings from the digestive tract. Of these 47 patients 23 were women and 24 men.

As many as 32 of the patients required blood transfusions because of such bleedings. Heavy losses of blood occurred particularly in patients with the severe form of the disease. Severe bleeding has, however often occurred even in patients who, judging from laboratory studies, had the mild form of disease (see Table 14, page 87)

One patient with a firm diagnosis of von Willebrand's disease of the mild type (34 III.2 IL) died from spontaneous gastric bleeding. He died after a few days profuse bleeding despite administration of Fraction I-O (3x100 ml) and several blood transfusions. 40 1.2 GW also with mild von Willebrand's disease, is said to have died at home in gastro-intestinal bleeding. A third patient, who had died from gastric bleeding (100 I 1 GL) was the maternal grandfather of a proband with known von Willebrand s disease. He had also had other bleeding symptoms, and there is reason to assume that he had had the same haemorrhagic disease as the son of his daughter

Four other persons included in this series as relatives of patients with known von Willebrand's disease, are said to have died from gastric bleeding. In one of them (76 II.3 KGA) the death certificate confirmed the cause of death. In the other three cases (34 I 1 KL and II 1 HE, 63 II-6 JL) hospital records were unavailable.

One of our patients (11 II.1 GB) had for many years had frequently recurring severe and disabling gastric bleeding, and he had been granted a sick-pension.

Only rarely was it possible to demonstrate an ulcer or some other local cause of the gastro-intestinal bleeding. Most of the patients had been examined roentgenographically at the time of the bleeding of the stomach and duodenum and often also of the oesophagus and colon and occasionally of the small intestine. The results of roentgen examination of 24 of the patients who had required blood transfusions because of gastric bleeding are given in Table 17

Post mortem findings were known only in respect of two of the patients who had died from gastric bleeding. One of them (34 III.2 IL) was found to have suspected callous ulcer (post mortem changes made examination difficult): the other (100 I 1 GL) had widened blood vessels near the pylorus, otherwise no demonstrable source of bleeding.

11 II 1 GB, who had been disabled for many years by gastric haemorrhage, was finally subjected to surgical exploration, but no source of bleeding was found.

Table 17

Roentgen findings in 24 Swedish patients with von Willebrand s disease, who had received blood transfusions or had died because of gastro-intestinal bleeding

	Number of patients
Ulcer demonstrated	2
Ulcer suspected	1
Deformation of bulb, gastritis or gastroduodenitis	5
Gastric polyp	1
Nothing remarkable in part of digestive tract examined	15

The age distribution of the patients in our series at the time of consultation or admission to hospital because of gastro-intestinal bleedings is given in Fig. 5, page 106. The age distribution was much wider than that of other types of bleeding and bleeding was most common between the ages of 30 and 60 years. In the adult this type of haemorrhage was more common in men (21 patients) than in woman (14 patients).

Menorrhagia and metrorrhagia

Menorrhagia is one of the commonest haemorrhagic symptoms among women with von Willebrand's disease. The frequency varies considerably from author to author. Macfarlane and Simpkiss (1954) described a large family with 7 women but with only one with profuse menstruations. Cornu (1965) gave a frequency of 75 % for remarkable genital bleedings and Buchanan and Leavell (1956) 51 % of meno-metrorrhagia among women with von Willebrand's disease. The wide variation in the frequency is probably due to differences in opinion among the physicians and among the patients as to what should be regarded as severe bleeding. Anaemia, if present, is useful in deciding this point. It appears that no exact measurements have been made of the amounts of blood lost. It is of interest to compare the patients with von Willebrand's disease and our normal series, where 25.2 % of the women above 15 years reported recurrent profuse menstrual flow. 8.6% had sought medical advice because of such symptoms.

According to several authors, the profuse menstrual flow occurs, above all, among young women during the first few years after menarche (Waller & Gross 1964, Henrion 1965 and van Creveld & Shellekens 1969), and a search of the literature for life-threatening menorrhagia showed that most such cases occurred in the beginning of the period of reproduction.

Very serious profuse menstrual flow has been described by various authors (B. Jacobsson 1957, Sharp & Ellis 1960, Henrion 1965, Hill & Taylor 1968, Larrieu et al. 1968, van Creveld & Shellekens 1969, Gomperts et al. 1969 and J. Jürgens 1969). In some cases the symptom was so refractory that the women were finally subjected to hysterectomy (B. Jacobsson 1957, Sharp & Ellis 1960, Hill & Taylor 1968 and Larrieu et al. 1968).

With available therapeutic methods fatal menorrhagia is rare, but such cases have been described by e.g. Fowler (1937), J. Jürgens (1969) and von Willebrand (von Willebrand, Jürgens & Dahlberg 1934) whose first patient, Hjördis S., died from her fourth menstruation.

Present series

82 women with a firm diagnosis of von Willebrand's disease reported considerable menorrhagia or metrorrhagia. The frequency of this symptom in women above 15 years was 60.1 %.

The patient's age at the time of treatment and blood transfusion are given in Fig. 5, page 106. Our figures thus corroborate the view by Waller and Gross (1964) and Henrion (1965), for example, that menorrhagia is severest the first few years after menarche.

29 women (inclusive two, whose diagnosis had not been confirmed by laboratory examinations) were given blood transfusions because of meno-metrorrhagia.

Three girls with the severe form of von Willebrand's disease (I V:5 BT, 4 IV.2 GB and 16 III.1 AKZ) had had such severe and often life-threatening menorrhagia so early that they had been subjected to hysterectomy or roentgen castration at 14, 15 and 16 years, respectively. One patient (36 III.19 KB) died from menorrhagia, which persisted continuously for 5 months after menarche. That death dates back to 1922, i.e. before von Willebrand's disease had been described as such. The girl was a cousin of the mother of one of our patients with the severe form of von Willebrand's disease (36 IV.2 IN).

The most serious episodes of menorrhagia occurred in patients with the severe form of the disease. But fairly profuse menstrual flow was not uncommon among other cases; at least half of the women in our series who had received blood transfusions because of menorrhagia had the mild form of von Willebrand's disease.

The course of the cases of menorrhagia that required blood transfusions is given in Table 18. Here, then, there was a tendency of the disorder, even of the severe form, to improve already before the patients had reached 20 years of age, spontaneously, after parturition or after treatment with sex hormones.

Table 18

Swedish patients with von Willebrand's disease requiring blood transfusions because of menorrhagia or metrorrhagia.

Course	Type of von Willebrand's disease		
	Severe	Mild	Total
	Number of cases	Number of cases	Number of cases
Death (14 years)	1[1])		1[1])
Hysterectomy or roentgen castration because of bleeding before 20 years	3		3
Hysterectomy or roentgen castration because of bleeding at 20–40 years	1	4	5
Severe bleeding symptoms during entire period of reproduction		3	3
Severe bleeding symptoms the first years after menarche with considerable improvement			
before 20 years	7	5	12[2])
at 20–30 years	1	2	3
Occasional severe bleeding (31 years)		1	1
Severe bleedings because of myoma near the menopause		1[1])	1[1])
Sum	13	16	29

[1]) von Willebrand's disease not confirmed by laboratory tests

[2]) improvement spontaneous 5 cases
after parturition 3 "
after treatment with progesterone or p-pills" 4 "

Post partum haemorrhage

von Willebrand pointed out (von Willebrand, Jürgens & Dahlberg 1934) that the women in his Åland series bled less at parturition than what might have been expected. Buchanan and Leavell (1956) in their compilation of published series found an overall frequency of 10.5 % of profuse post partum bleeding for women of all ages.

In patients with von Willebrand's disease, then, bleeding complications are less common than what one might à priori expect. One of the most important explanations for this is that, as in normal pregnant women (Kasper et al. 1964, Rutherford et al. 1964 Nilsson & Kullander 1967) the AHF-content increases during pregnancy also in patients with von Willebrand's disease.

This was first observed by van Creveld et al. (1962) who found an increase of the AHF in one woman from 1 % before to 15 % towards the end of pregnancy (33rd week). At the same time the bleeding time by the technique of Duke had become normal from 25 minutes before pregnancy to 3 minutes in the 33rd week.

Similar observations have later been made by e.g. Strauss and Diamond (1963), Kasper et al. (1964), Winckelmann et al. (1967) and Walker and Dormandy (1968). Occasionally however the AHF-content and bleeding time in patients with von Willebrand's disease with low values before pregnancy remained low throughout pregnancy (Winckelmann et al. 1967 Walker & Dormandy 1968). In such cases the women lost large amounts of blood at delivery

The improvement of the values towards the end of pregnancy soon disappears after delivery (Strauss &

Diamond 1963 Winckelmann et al. 1967). This means that the risk of bleeding is less on the day of parturition than somewhat later

Thus, though the frequency of heavy bleeding is not so very high, when it does occur it is often severe and may persist with exacerbations for several months. Examples of such cases have been described by Mc Cammon (1967), Winckelmann et al. (1967) and Hill and Taylor (1968). Occasionally the bleeding could only be controlled by hysterectomy (Hill & Taylor 1968) or radiotherapy (Mc Cammon 1967) Fatal bleeding at delivery has been reported by von Willebrand (1926), Levy (1947) and by Klesper and Achenbach (1957).

Bleeding at and after delivery may be normal on one occasion and abnormal on another (Imerslund 1949 Raccuglia & Neel 1960, Strauss & Diamond 1963, Henrion 1965 and Hill & Taylor 1968). As a rule the first delivery appears to involve the greatest risk. Delivery by Caesarean section may cause loss of just as much blood as delivery by the normal route (Hill & Taylor 1968).

The risk of bleeding has often been judged from determinations of the AHF and bleeding time and from the patient's history Horowitz and O'Leary (1965) claim that if the bleeding time by the technique of Duke is normal and the AHF is more than 20 / and "if the patient has previously encountered no difficulty in similar situations there is no reason statistically to expect bleeding complications at parturition. Walker and Dormandy (1968) ascribed the risk of bleeding above all to the low AHF-values and feel that an AHF of 30 or less at the time of parturition is an absolute indication for prophylaxis with substitution of factor VIII in the form of fresh frozen plasma, cryoprecipitate or freeze-dried factor VIII

Severe bleeding at parturition has, however been reported also in women with higher AHF (Henrion & Cornu 1964 McCammon 1967)

Present series

The frequency of severe bleeding at delivery among females above 15 years in the present material was 23.3 ‰ compared with 19.5 / in the normal series. As previously mentioned (page 86), the high figure in the normal series can be explained partly by the fact that most of the women in that series were mothers of children seen at a pediatric outpatient department and had thus been parous. Of those parous women with von Willebrand's disease in the present series the frequency of profuse bleeding at delivery was 34.5 ‰.

In 6 of our women with von Willebrand's disease the changes in AHF and bleeding time during pregnancy were recorded (Table 19).

Thirteen of the women in our series had bled on all together fourteen occasions so heavily at or after delivery as to require blood transfusions. On 8 occasions the bleedings had occurred at first delivery and in 6 this was the only delivery The bleeding often occurred late and it was sometimes much prolonged with exacerbations several weeks after parturition (see Fig. 1).

Three of these women had the severe form of von Willebrand's disease with AHF of less than 20 and a bleeding time by the method of Duke of more than 30 minutes. Delivery of two of them (2 III.2 YL and 36 IV.2 LN) had caused severe and prolonged bleeding despite prophylatic treatment with Fraction I-O and fresh plasma. None of the other women in the series with such severely abnormal values had given birth.

Judging from laboratory studies, 10 of the 13 women who had received blood transfusions at or after delivery

Table 19

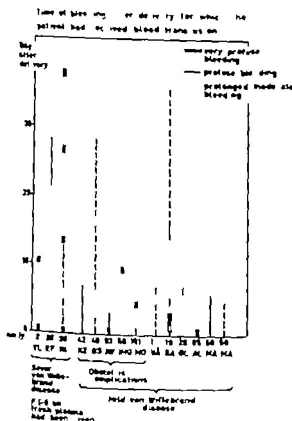
Changes of AHF-value and bleeding time during pregnancy

Patient	AHF before pregnancy	AHF during pregnancy	Duke bleeding time before pregnancy	Duke bleeding time during pregnancy
2 III.2 Y L	3 – 4	10 (m VIII)	60'	22' (m VIII)
22 II 1 I D	15 – 39	61 (m VII)	28'[1])	14 [1]) (m VII)
26 III 2 E F	17		60'	11 18' (m IX)
36 IV.2 LN	2	4 8 (m IX)	55 – 63'	30' (m IX)
42 III 19 I H			18'	2'33" (m VI)
III.34 K S	35 45	48 (m VI)	1 – 8'	6'-8' (m VI)

[1]) bleeding time according to Ivy

had the mild form of von Willebrand's disease A contributory cause of the bleeding in one (4 III.27 KZ) of these cases was a large vaginal rupture In three cases the hospital records contained notes about pieces of

Fig 1



placenta or decidual rests t inspection or after uterine curettage (49 IV 3 GS, 58 III 1 AMG and 101 II 1 MO). One woman with the mild form of von Willebrand's disease (53 III 2 IW) had bled profusely t Caesarean section because of threatened cervical rupture In that case the bleeding had occurred immediately after the operation and the patient had gone int shock. I 5 other cases mild von Willebrand disease was the only explanation that could be found for the bleeding One of these women (19 III I SA) had bled very profusely and required 21 blood transfusions

In this connection it might be mentioned that 4 8 % of the females bove 15 years in the control series received blood transfusions t delivery The corresponding figure for the women with mild von Willebrand disease was 8 6%.

Bleeding at abortion

Spontaneous abortion has been described a common in patients with von Willebrand s disease (Buchanan & Leavell 1956 Horowitz & O Leary 1965 nd McCammon 1967) Of Horowitz and O'Leary se es of 25 women with on Willebrand disease, 11 had been pregnant on all together 34 occasions and 9 of the pregnancies had terminated in spontaneous abortion.

Profuse bleeding following spontaneous or induced abortion has been reported by H dley and Nussbrecher (1935) and Lelong and Soulier (1950) but has apparently not been life-threatening

Present se ie

In view of the reports by Horowitz and O'Leary the women in our series were asked whether they had had spontaneous abortions and, if so, whether they had lost much blood. The records of 9 of 86 parous women with a f rm diagnosis of von Willebrand' disease contained notes about spontaneous abortion. Three (32 III.2 SN, 59 II.2 SA and 100 II 2 MS) had had respectively 2, 4 and 3 abortions but also respectively 2, 4 and 4 live births. The other women had borted spontaneously only once. One of them (65 III 1 BS) had repeatedly sought medical advice because of involuntary sterility – On the whole, the frequency of spontaneous abortions in our series was not remarkably high I Swedish women without known bleeding disease the frequency of spontaneous abortions has been estimated t 10 – 12 (Pettersson 1970).

A profuse loss of blood at spontaneous bortion was reported by all together 7 women in the present series But in two of them (42 II 2 GÅ and 73 I 2 EA) the diagnosis had not been confirmed by laboratory examinations Bleeding was most troublesome in 4 II GÅ, who had Hb according t Sahli of less than 10 (less than 1 6 g/100 ml) and the erythrocyte count fell to 960 000 mm³ The patient had not only uterine bleeding but lso severe nose-bleeding, and it is not clear f om the notes in the patient records whether uterine or the nose-bleeding had caused the greater loss of blood

One woman (86 III 1 AMÅ) reported that she had bled heavily at induced abortion but her hospital records could not be traced

Ovarian bleeding

A form of b eeding that has received less space in the literature on von Willebrand s disease is ovarian blee ding or corpus luteum bleeding. Sharp and Ellis (1960) described a woman who had been admitted twice and operated upor because of haemoperitoneum in association with ruptured ovarian follicles On neither occasion was the loss of blood severe. The patient had AHF of 18 – 34 and the bleeding time by the method of Duke was repeatedly more than 15 minutes. Other similar cases have been briefly mentioned by Koch et al. (1957), Wake and McClure (1965) and Winckelmann et al. (1967). The two last mentioned authors give data on the AHF which was 5 and less than 1 and the bleeding time was more than 20 minutes in both

Present series

Ovarian or follicular bleeding had been diagnosed in 9 of the present patients, including 5 on repeated occasions In typical cases the patients had fallen ill intermenstrually with more or less severe abdominal pain and often decreasing Hb. Examination had revealed a rounded lump at the site of one of the ovaries or a swelling in the small pelvis. In three cases the diagnosis was confirmed by laparotomy In none of the cases had laparoscopy been performed.

The ovarian bleeding had most often occurred early in reproductive life (see F g 5 page 106) and in 8 of 9 cases the women had the severe form of von Wille brand's disease In 5 patients blood transfusions were given because of such bleeding One woman (23 II 4 SW), aged 19 years, was operated upon for evacuation of corpus luteum bleeding. She continued to bleed hea ily after the operation and died a few days later despite repeated transfusions One woman (10 III 1 MCA) who had been treated with p-pills for some years had severe ovarian bleeding when she stopped using the pills Another (16 III 1 AKZ), who had been subjected to hysterectomy afterwards had such frequently recurrent and troublesome ovarian bleedings that she had continuously to take p-pills which ga e improvement.

In the description of ovarian bleeding it might be of interest to mention a relatively high frequency of operations for ovarian cysts in our patients It is quit possible that several of these cysts had formed as consequence of follicular bleeding

Bleeding from urinary tract

Haematuria is not common in von Willebrand's disease and, judging from published cases, it is seldom severe. According to J Jürgens (1969), however hae maturia in von Willebrand s disease is just as common as in haemophilia and in three of his cases it was the indication for blood transfusions. Estren, Medal and Dameshek (1946) gave a frequency of 6.3 and Buchanan and Leavell (1956) gave 7.5 / for men and 2 % for women.

Present series

In our series haematuria was observed in 18 cases (6.8).

Only in one (9 III 1 ES) had it caused noticeable anaemia (Hb 7.5 g/100 ml) In two (7 III.1 MA and 8 II 1 RB) blood transfusions had been given, but evidently mainly to stop the bleeding. Recurrent gross haematuria had occurred in 4 (13 III.2 SE, 15 II 4 KS, 51 II.2 MN and 82 II.1 AT) but in none of them had the loss of blood been severe.

In one (7 III.1 MA) of the patients with gross haematuria the bleeding had on one occasion probably been due to stone. In the other cases no explanation could be offered for the bleeding. Urography had revealed nothing remarkable; nor had cystoscopy in those cases examined.

In three cases (13 III.2 SE, 15 II 4 KS and 82 II.1 AT) it was because of haematuria that the patients had been referred to the coagulation laboratory for investigation.

Joint bleeding

Joint bleeding is not common in von Willebrand's disease, which in this respect differs from classical haemophilia. This difference was pointed out already by von Willebrand and Jürgens (1933 a). Low figures have also been reported by other authors. Thus Estren, Medal and Dameshek (1946) gave 12.5 , Biggs and Macfarlane (1957) 8 / and Buchanan and Leavell (1956) 12.5 in men and 5 / in women.

When joint bleedings occur they usually do so before puberty (Deshayes et al. 1967), and practically only in patients with the severe form of the disease. The AHF is low in most cases less than 20%. Traumatic haemarthrosis, however has occurred also in patients with higher values (Marx & Jean 1964 Deshayes 1967). Many of the patients with joint bleedings had had extremely low AHF values down to 1 – 2 and even to

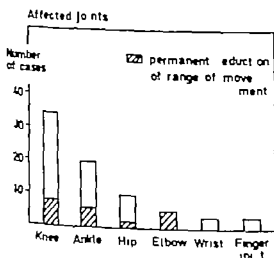
less than 1 (Nevanlinna, Ikkala & Vuopio 196_, Verstraete 1963, Ascari, Barbieri & Gobbi 1964, Larrieu & Bancalari 1965, Wale & McClure 1965, Bowie et al 1967, Castaldi et al. 1967 and Walker & Dormandy 1968). Permanent joint deformations have been reported in only a few cases (Achenbach et al. 1959, Ascari, Barbieri & Gobbi 1964, Mauro et al. 1969, Hagedorn 1971)

Present series

Joint bleeding had been diagnosed in 18 cases and suspected in a further 4, together constituting 8.3 of the series of patients with a firm diagnosis of von Willebrand's disease.

The knees and the ankles had been involved most often (see Fig. 2)

Fig



The bleedings had occurred most often in childhood and adolescence (Fig. 5, page 106)

Of the 18 patients who had had clear symptoms of joint bleeding, 16 had the severe form of von Willebrand's disease. The bleedings had usually occurred after trivial or unknown trauma. Only in two cases had typical joint bleeding occurred in patients (14 III 4 IJ and 42 III 25 SN) with the mild form of von Willebrand's disease, in both of the cases after substantial trauma (see page 91)

In 7 patients the range of movement of joints had been permanently decreased. All had a bleeding time of more than 30 minutes by the method of Duke. The mean AHF in 3 of them had been less than 5 and between 5 and 10 in 3 others. For the 7th who died in 1951 the AHF had never been determined. Three (8 II 1 RB, 9 III 1 ES and 27 III 4 KR) of these 7 patients had such joint changes that they were handicapped, though not disabled.

In all of the patients with severe joint bleeding, especially in those with permanent reduction of range of movement, roentgen examination had shown more or less severe changes with reduction of cartilage of the type seen in haemophilia.

32 patients (including 28 who are still living) in the Swedish series had the severe form of von Willebrand's disease. 16 of them clearly had joint bleeding. A further one (36 IV _ IN) had had troublesome swelling of the joints as a child, presumably due to her haemorrhagic disease. Among such severe cases haemarthrosis is a common symptom of roughly the same frequency and severity as that in patients with corresponding AHF level in haemophilia. In none of our patients was the AHF so low (less than 1 _) as in the haemophiliacs in Ramgren's and Ahlberg's series (1962 and 1965) regarded as severely ill.

Unusual forms of bleeding

Present series

Unusual forms of bleeding, which had occurred in at most three cases in Swedish patients with a firm diagnosis of von Willebrand's disease are listed in Table 20.

Table 20

Unusual types of bleeding occurring in at most 3 cases in Swedish patients with a firm diagnosis of von Willebrand' disease

	Number of cases
Intracranial bleeding	3
Ey_ bleeding	3
Pleural bleeding	3
Cortal bleeding	3
Haemorrhoidal bleeding	3
Bleeding from dental abscess	1
Cephalic haematoma (at birth)	1
Bleeding from spontaneously perforated abscess	1
Umbilical bleeding (neonatal)	1
Bleeding from oesophagus in cardiospasm	1
Retroperitoneal bleeding	1
Vaginal bleeding (at 15 months of age)	1

Ovarian bleeding

A form of bleeding that has received less space in the literature on von Willebrand's disease is ovarian bleeding or corpus luteum bleeding. Sharp and Ellis (1960) described a woman who had been admitted twice and operated upon because of haemoperitoneum in association with ruptured ovarian follicles. On neither occasion was the loss of blood severe. The patient had AHF of 18 – 34 and the bleeding time by the method of Duke was repeatedly more than 15 minutes. Other similar cases have been briefly mentioned by Koch et al. (1957), Wake and McClure (1965) and Winckelmann et al. (1967). The two last mentioned authors give data on the AHF which was 5 and less than 1 and the bleeding time was more than 20 minutes in both.

Present series

Ovarian or follicular bleeding had been diagnosed in 9 of the present patients, including 5 on repeated occasions. In typical cases the patients had fallen ill intermenstrually with more or less severe abdominal pain and often decreasing Hb. Examination had revealed a rounded lump at the site of one of the ovaries or a swelling in the small pelvis. In three cases the diagnosis was confirmed by laparotomy. In none of the cases had laparoscopy been performed.

The ovarian bleeding had most often occurred early in reproductive life (see Fig. 5 page 106) and in 8 of 9 cases the women had the severe form of von Willebrand's disease. In 5 patients blood transfusions were given because of such bleeding. One woman (23 II-4 SW), aged 19 years, was operated upon for evacuation of corpus luteum bleeding. She continued to bleed heavily after the operation and died a few days later despite repeated transfusions. One woman (10 III 1 MCA) who had been treated with "p-pills" for some years had severe ovarian bleeding when she stopped using the pills. Another (16 III 1 AKZ), who had been subjected to hysterectomy afterwards had such frequently recurrent and troublesome ovarian bleedings that she had continuously to take "p-pills" which gave improvement.

In the description of ovarian bleeding it might be of interest to mention relatively high frequency of operations for ovarian cysts in our patients. It is quite possible that several of these cysts had formed as a consequence of follicular bleeding.

Bleeding from urinary tract

Haematuria is not common in von Willebrand's disease and, judging from published cases, it is seldom severe. According to J. Jürgens (1969), however haematuria in von Willebrand's disease is just as common as in haemophilia and in three of his cases it was the indication for blood transfusions. Estren, Medal and Dameshek (1946) give a frequency of 6.3 and Buchanan and Leavell (1956) gave 7.5 for men and 2 for women.

Present series

In our series haematuria was observed in 18 cases (6.8).

Only in one (9 III 1 ES) had it caused noticeable anaemia (Hb 7.5 g/100 ml). In two (7 III.1 MA and 8 II.1 RB) blood transfusions had been given, but evidently mainly to stop the bleeding. Recurrent gross haematuria had occurred in 4 (13 III.2 SE, 15 II.4 KS, 51 II.2 MN and 82 II 1 AT) but in none of them had the loss of blood been severe.

In one (7 III 1 MA) of the patients with gross haematuria the bleeding had on one occasion probably been due to stone. In the other cases no explanation could be offered for the bleeding. Urography had revealed nothing remarkable; nor had cystoscopy in those cases examined.

In three cases (13 III.2 SE, 15 II 4 KS and 82 II.1 AT) it was because of haematuria that the patients had been referred to the coagulation laboratory for investigation.

Joint bleeding

Joint bleeding is not common in von Willebrand's disease, which in this respect differs from classical haemophilia. This difference was pointed out already by von Willebrand and Jürgens (1933 a). Low figures have also been reported by other authors. Thus Estren, Medal and Dameshek (1946) gave 12.5 %, Biggs and Macfarlane (1957) 8 % and Buchanan and Leavell (1956) 12.5 % in men and 5 % in women.

When joint bleedings occur they usually do so before puberty (Deshayes et al. 1967), and practically only in patients with the severe form of the disease. The AHF is low in most cases less than 20%. Traumatic haemarthroses, however has occurred also in patients with higher values (Marx & Jean 1964, Deshayes 1967). Many of the patients with joint bleedings had had extremely low AHF values down to 1 – 2 % and even to

AGE DISTRIBUTION OF BLEEDING SYMPTOMS

It is clear from the foregoing that bleeding symptoms were most common in childhood and adolescence.

Fig 4–5 shows the age distribution of the patients at the time of medical or dental treatment for different types of bleeding. The number of occasions on which the patients received blood transfusions are indicated.

The bleeding tendency in childhood was dominated by bleeding from the nose, oral cavity and throat. After puberty bleeding from these areas rarely required blood transfusions.

For natural reasons uterine bleeding did not occur until after puberty. Menorrhagia, however, often appeared soon after menarche and medical consultation because of such bleeding was more common between the ages of 11 and 15 years than during any other 5 year period.

Gastro-intestinal bleeding was most common in the 30–45 year age group and was also fairly common among older persons.

Fig 4

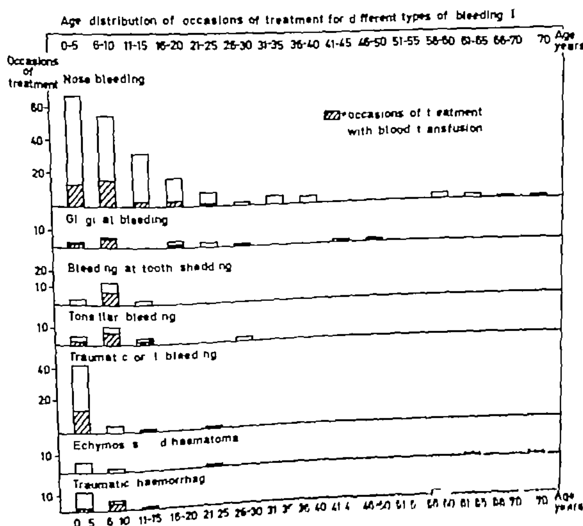
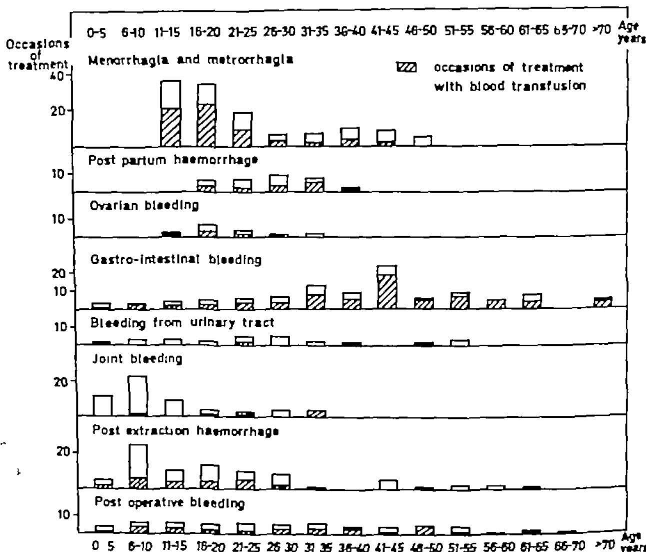


Fig 5



INITIAL SYMPTOMS, DIAGNOSTIC SYMPTOMS AND AGE AT ONSET OF FIRST SYMPTOM AND DIAGNOSIS

The initial and diagnostic symptoms of the probands are summarised in Tables 24 and 25

Here the term initial symptom is to be understood as the first bleeding symptom observed by the patient or by his or her parents. The diagnostic symptom is the bleeding symptom, that had indicated investigation at a coagulation laboratory where von Willebrand's disease was diagnosed.

The commonest initial symptoms were nose bleeding and ready bruisability whether von Willebrand's disease was of severe or mild type An increased bleeding tendency in severe cases sometimes was revealed very early *e.g* by bleeding from the umbilical cord or after triple vaccination. In 7 cases of the mild type the bleeding tendency was not observed until after tooth extraction.

The diagnostic symptom was in 20 cases uterine bleeding (menorrhagia or heavy bleeding at delivery) and in two cases bleeding after hysterectomy This may help to explain why females were so predominant among the probands (see page 84). In severe von Willebrand's disease the diagnosis was otherwise mostly made in childhood after symptoms such as nose-bleeding, ready bruisability or a general bleeding tendency In probands with the mild form of von Wille-

Table 24

Initial symptoms in Swedish probands with von Willebrand's disease

Symptom	Type of von Willebrand's disease: Severe number of cases	Mild number of cases	Sum
Nose-bleeding	12	28	40
Bruisability	5	13	18
Post-extraction haemorrhage	1	7	8
Anaemia	1	3	4
Traumatic oral bleeding	2		2
Gastrointestinal bleeding	1	1	2
Haematuria			2
Bleeding after cuts	1	1	2
Bleeding after triple vaccination	2		
Postoperative haemorrhage	1	1	
Menorrhagia		1	1
Umbilical bleeding	1		1

Table 25

Diagnostic symptoms in Swedish probands with von Willebrand's disease

Symptom	Type of von Willebrand's disease: Severe number of cases	Mild number of cases	Sum
Menorrhagia	7	10	17
Postoperative haemorrhage	1	11	12
Nose-bleeding	4	7	11
Gastrointestinal bleeding	1	10	11
Post-extraction haemorrhage	1	10	11
Traumatic oral bleeding		3	3
Urinary tract bleeding	1	2	3
Bleeding at delivery		3	3
Bruisability	3		3
General bleeding tendency	3		3
Anaemia	1	1	2
Gingival bleeding	1		1
Tonsillary bleeding	1		1
Bleeding after cuts	1		1
Bleeding after triple vaccination	1		1
Joint bleeding	1		1

brand's disease the diagnosis often remained concealed until bleeding was provoked by tooth extraction, for example, or other operations. In 10 patients it was relatively late gastro-intestinal bleeding, which led to the examination resulting in the diagnosis.

The ages of the probands at the time of the initial symptoms and of the diagnosis are given in Tables 26 and 27. It was often not possible to date the initial symptom exactly, especially in the mild cases of von Willebrand's disease. In such cases the onset was described as having occurred in childhood or adolescence. It was, however, evident that the severe form of von Willebrand's disease nearly always produced manifestations in early childhood, while the bleeding tendency in the *mild form of von Willebrand's disease often appeared* fairly late. The diagnostic ages were therefore, on the average, much higher in the mild cases. With increasing spread of knowledge of von Willebrand's disease the severe form was practically always diagnosed before the patient was 10 years of age.

Table 26

Age at first bleeding symptom in Swedish probands with von Willebrand's disease

Years	Type of von Willebrand's disease: Severe number of cases	Mild number of cases	Sum
0–5	24	9	33
6–10	1	5	6
Childhood	2	20	22
11–15		2	2
16–20		2	2
Adolescence		10	10
21–30		6	6
31–40		2	2
>40		1	1

Table 27

Age at diagnosis in Swedish probands with von Willebrand's disease

Years	Type of von Willebrand's disease: Severe number of cases	Mild number of cases	Sum
0–5	6	7	13
6–10	3	7	10
11–15	7	4	11
16–20	7	3	10
21–30		8	8
31–40	4	11	15
>40		17	17

DIAGNOSIS

In the present investigation the diagnosis of von Willebrand's disease was based mainly on the patient's history on investigation of the family and on values found for AHF and the bleeding time according to Duke and to Ivy As a supplementory examination method determinations were made of platelet adhesiveness by the method of Salzman. Laboratory tests were made for all probands and most of the relatives on repeated occasions. Many of the probands were examined for AHF increase and shortening of the bleeding time following administration of Fraction I–O or fresh plasma.

The criteria for the diagnosis are given on page 13. According to the patient's history the bleeding tendency was classified as:

+++ severe
++ moderately severe
+ slightly increased
– no increase or no certain increase

The classification of the bleeding tendency in each of the subjects examined is given in Table 2 in column *Sum*

History

The patient's history was judged mainly from the frequency and severity of bleeding symptoms and the number of forms of bleeding in the individual case. Types of bleeding common among normals (page 85) were not considered so informative as haemorrhage of the type rarely seen in persons without any known bleeding disease Due allowance was made for the fact that in children bleeding tendency had not had time to become manifest to the same extent as in adults.

Evaluation of the bleeding tendency in this way must, of course, be largely dependent on the subjective evaluation of the individual giving his history the person filling in the patient's card and the person summarising the history It was nevertheless considered warranted to summarise the findings in order to enable comparison between the anamnestic findings and the results of various laboratory tests.

AHF

The AHF-level may be influenced by several factors For example, physical exertion raises the AHF (Rizza 1961 Egeberg 1963, Ikkala, Myllylä and Nevanlinna 1964, Cornu 1965). Also mental stress may raise the AHF (Owren 1965). A stress-like reaction can be produced experimentally by administration of epinephrine and an increased AHF after injection of epinephrine has been observed by Egeberg (1963), for example. This observation may be important when examining children in whom sampling often causes anxiety An increase of the AHF has also been found in women during pregnancy (page 95) and during treatment with contraceptive pills (Egeberg & Owren 1963 Nilsson & Kullander 1967 Özsoylu & Corbacioglu 1967a and b). Nilsson (1959) has shown that the AHF is, on the average, higher in women after the menopause than otherwise. Infections have also been found to be associated with an increase of the AHF (Egeberg 1962, Goldenfarb et al. 1970).

A slow flow of blood at sampling may result in artificially low AHF values (Penick & Brinkhous 1956). Further the AHF-content of the plasma decreases rapidly after sampling unless the samples are examined immediately or immediately frozen at very low temperatures (Penick & Brinkhous 1956, Rapaport, Ames & Mikkelsen 1959). Those samples from our patients, which were sent to the coagulation laboratory from distant places were centrifuged immediately and the plasma was frozen in carbon ice and was always still frozen on its arrival at the laboratory Nevertheless the AHF-values were more often unexpecedly low in these samples than in samples obtained directly at the coagulation laboratory with better freezing facilities.

The considerations set forth above may help to explain why the AHF-values sometimes varied from one occasion to another mainly in patients with mild von Willebrand's disease. More or less widely varying AHF-values have also been reported by several authors (Arrants, Jordan & Newcomb 1962, Eriksson, 1962, Strauss & Bloom 1965, Abildgaard et al. 1968, Larrieu et al. 1968 and Papayannis, Wood and Israëls 1971).

It is possible that the AHF-values are also influenced by variation in the severity of the disease owing to factors other than those referred to above. In elderly patients with von Willebrand's disease the bleeding tendency diminishes (page 105) and the AHF tends to increase with age, as may be seen from the following statistical study

AHF after more than 5 years

Of those cases in the Swedish von Willebrand-series which were re-examined after more than 5 years, 33 showed an increased AHF and only 16 a lower value. This increase was significant ($p < 0.05$). The interval between the examinations varied between 5 and 11 years and was, on the average, 6.5 years. The average increase during this period was 7 %. The increase was not limited to certain AHF-levels, but was noted in patients who had originally had a high AHF level as well as in those who had originally had a low AHF level.

Bleeding time by the method of Duke

Determination of the bleeding time according to Duke is a relatively crude method. Buchanan and Leavell (1956), for example, have stressed the frequently considerable differences between values found for samples obtained on one and the same occasion from both ears, and such differences were seen also in our investigations.

Wide fluctuation in the bleeding time according to Duke in von Willebrand's disease from one occasion to another has often been reported (Soulier & Larrieu 1954, Cornu et al. 1961, Lemoyne & Larrieu 1967, Abildgaard et al. 1968 and others). We have seen such variation in the patients with mild von Willebrand's disease, but in patients with a severe bleeding tendency the bleeding time according to Duke has nearly always been prolonged to more than 30 minutes. The observed fluctuation may be partly explained by the sources of error of the method. But also the bleeding time, like the AHF, is influenced by pregnancy, for example, (see page 95). There may also be reason to assume that the variation of the values reflects fluctuation of the severity of the disease from one occasion to another (see page 42 and 72, 51 III.3 SÅN).

Bleeding time by the method of Ivy

In 1941 Ivy (Ivy, Nelson & Bucher 1941) described a method for determining the bleeding time of the lower arm during venous occlusion by a sphygmomanometer cuff wrapped around the upper arm. In its original form the method was more sensitive than Duke's for diagnosing certain bleeding diseases. It has, however, since been considerably improved by modifications described by Borchgrevink and Waaler 1958 and later described by Nilsson, Magnusson and Borchgrevink (1963). With these modifications the method is much more sensitive than Duke's and it has been shown by Silwer and Nilsson (1964), for example, that it can reveal an increased bleeding tendency even in mild cases of von Willebrand's disease.

The procedure, however, is difficult to standardise because of, among other things, the difficulty of producing a transverse incision of standard length and depth on the forearm. The character of the incision depends on the thickness of the skin and the elasticity of the tissues and the sharpness of the surgical blade. The bleeding time also depends on the way the blood drops are absorbed from the wound. Inadvertant contact with the edges of the incision can open the blood vessels and then bleeding may continue for more than 15 minutes even in normals. On the other hand, too cautious an absorption may result in blood drops persisting on the surface of the wound and coagulating with an artificially short bleeding time as a result. The difficulties encountered in the standardisation of the method are illustrated by, among other things, the fact that the coagulation laboratories in Malmö and Stockholm have obtained different normal values with an upper limit of 15 and 12 minutes, respectively.

In von Willebrand's disease determination of the bleeding time according to Ivy has often given different results from one occasion to another just as when the method of Duke was used (Verstraete 1963, Ascari, Barbieri & Gobbi 1964, Cornu 1965, Castaldi et al. 1967, Abildgaard et al. 1968 and Papayannis, Wood & Israëls 1971). Such variation sometimes occurred also in the mild cases in our series.

Platelet adhesiveness according to Salzman

Determinations were made of the platelet adhesiveness according to the method of Salzman in two materials. The first, limited material was collected at an international investigation in 1967. That investigation was carried out at the request of The International Committee on Haemostasis and Thrombosis when coagulation laboratories in various countries determined the platelet adhesiveness according to Salzman in order to decide the diagnostic value of the procedure in von Willebrand's disease. The Coagulation laboratory in Malmö took part in that investigation and samples were obtained from all together 11 persons with a strictly standardized material obtained from E. Salzman himself. The examination was carried

out by laboratory assistants who had been specially trained and [illegible] were well versed with the method.

Of the 61 persons examined, 32 had von Willebrand's disease that had previously been diagnosed from the [illegible] histories and determination of the AHF and bleeding time according to Duke and Ivy. The normal material [illegible] 29 persons, mainly laboratory [illegible] to patients with von [illegible] persons in the normal [illegible] with von Willebrand's [illegible] evidence of the [illegible]

[illegible] are given in

[illegible] Salzman 61 per [illegible] von Willebrand's [illegible]

[illegible]	Number [illegible]	Number normal
0–?0		2
—		[illegible]
20	6	25

The two normal persons [illegible] of patients with von Willebrand [illegible] normal platelet adhesiveness.

In the determination of platelet adhesiveness according to Salzman we have encountered difficulties and sources of error especially of technical nature. The frequency of low values in both normals and affected persons proved higher in the beginning of the investigation period when the plastic tubes packed with glass beads were 11 cm long. Later on recommendation of Salzman, because of change in quality of the glass beads, the length of the tubes was increased to 13 cm. Then noticeably higher mean values were found and not infrequently values of more than 20 also in the affected persons. The rate of flow of the blood through the cannula proved to vary considerably with the caliber of the puncture needle, and with an increased flow rate the values found for platelet adhesiveness were much lower. An uneven flow which was slow in the beginning of sampling resulted in high values for platelet adhesiveness, even when the vacuum tube was satisfactorily filled after 45 seconds, when sampling was stopped.

Despite its imperfections the entire large material is presented here for the following reasons:

1. Thanks to its size the material may shed light on the question whether platelet adhesiveness is a factor of significance in von Willebrand's disease.
2. The investigation may reflect the value of the method and its limitations when performed by technical assistants who are not especially versed in the procedure.
3. The material has proved to be of certain interest in the calculation of correlations between platelet adhesiveness, on one hand, and historical findings, AHF content and bleeding times, respectively, on the other.

Results of evaluation of anamnestic data and of laboratory tests

Results of evaluation of anamnestic data and various laboratory tests for all persons examined, both healthy and affected, are given in Tables 29 and 30.

Table 29

Bleeding tendency as judged from historical data

	Number examined
+++	35
++	79
+	135
−	353

Table 30

Results of laboratory tests for all persons in the present material, both affected and unaffected.

Mean AHF	Number examined
0–20	30
21–40	83
41–64	163
≥65	309
Mean bleeding time by method of Duke	**Number examined**
>30'	36
11–30'	24
6–10'	67
≤5	457
Mean bleeding time by method of Ivy	**Number examined**
>30'	91
16–30'	139
≤15[1])	227
Mean platelet adhesiveness according to Salzman	**Number examined**
0–10	95
11–19	37
≥20	108

[1]) In (Stockholm ≤12'

Correlations

Anamnestic data and laboratory values have been studied for correlations by various authors (Achenbach 1960, Cornu et al. 1961 Nevalinna Ikkala & Vaopio 196_, Strauss & Bloom 1965 Larrieu et al 1968 and Papayannis, Wood & Israëls 1971).

In a series of 37 patients Larrieu et al for example found a good correlation of the anamnesis with AHF and bleeding time, respectively in severe cases of von Willebrand's disease. The correlation between anamnesis and the platelet adhesiveness according to Salzman was poorer The correlation between AHF and bleeding time according to Duke was good in the severe cases, but poor in moderate and mild cases. Platelet adhesiveness was always abnormal, but otherwise showed no quantitive relationship to AHF or bleeding time.

Papayannis, Wood and Israëls (1971) have studied laboratory values with rank correlations. They found platelet adhesiveness according to Salzman to be inversely correlated with bleeding time according to I y (23 pairs, $r = -0.69$ $p < 0.001$) and positively correlated with AHF (42 pairs, $r = 0.41$ $p < 0.005$). There was a negative correlation between AHF and bleed ng time, but this was not statistically significant.

Table 3

Correlation between historical data (bleeding tendency) and bleeding time according to Duke.

Mean bleeding time by method of Duke	Bleeding tendency + +	+	+	–
30'	31	5		
11 – 30'	1	16	5	2
6 10	1	18	23	25
≤ 5	2	70	101	314

Table 33

Correlation between historical data (bleeding tendency) and bleeding time according to Ivy

Mean bleeding time by method of Ivy	Bleeding tendency + + +	+ +	+	
> 30'	18	36	27	10
16 30'	3	33	54	4)
≤ 15 1)		4	17	16

1) in Stockholm ≤ 12'

Present series

In the present series anamnestic data on bleeding tendency were correlated with mean values for respectively AHF bleeding time according to Duke, bleeding time according to Ivy and platelet adhesiveness according to Salzman (see T bles 31 – 34).

The tables show a clear correlation between the examination findings and the history especially with the AHF and bleeding time according to Ivy The bleeding time according to Duke was nearly always very long in cases with a history of several and severe bleeding symptoms, but mostly normal in those with mild bleeding tendency and often even in those with moderate bleeding symptoms. Bleeding time [illegible] Ivy was sometimes prolonged to more than [illegible] in patients with no anamnestic blood [illegible] Determination of platelet adhesiveness [illegible] Salzman proved less valuable than [illegible] methods in the evaluation of the severity of [illegible]

Table 31

Correlation between historical data (bleeding tendency) and AHF

Mean AHF	Bleeding tendency –	–	1	–
0 – 20	25	4	26	18
21 – 40	4	35	57	66
41 – 64	4	36	50	56
≥ 65		3		

Table 34

Correlation between histor[illegible] (bleeding tendency) and platelet adhesiveness [illegible]

[illegible]

Mean platelet adhesiveness according to Salzman				
0 – 10				–
11 – 19	11	[illegible]	[illegible]	
≥ 20	4	[illegible]	[illegible]	
	[illegible]	[illegible]	[illegible]	

The correla[illegible] examination [illegible]

Table 35

Correlation between AHF and bleeding time according to Duke

Mean value of bleeding time according to Duke	Mean value of AHF % 0–20	21–40	41–64	≥65
>30′	25	7	2	
11–30′	3	12	4	5
6–10′		15	28	22
≤ 5	2	48	121	274

Table 36

Correlation between AHF and bleeding time according to Ivy

Mean value of bleeding time according to Ivy	Mean value of AHF % 0–20	21–40	41–64	≥65
>30′	16	34	31	10
16–30′	2	25	59	53
≤15′[1]		5	46	167

[1]) in Stockholm ≤ 12′

Table 37

Correlation between AHF and bleeding time according to Duke and Ivy (cases with bleeding time according to Duke of less than 30′ bleeding time according to Ivy not determined, not included).

Mean value of bleeding time according to	Mean values of AHF % 0–20	21–40	41–64	≥65
Duke >30′	25	7	2	
Duke <30′ Ivy >30′	3	27	29	10
Ivy 16–30′	2	25	59	53
Ivy ≤ 15[1])		5	46	167

[1]) in Stockholm ≤ 1

Table 38

Correlation between AHF and platelet adhesiveness according to Salzman

Mean value of platelet adhesiveness according to Salzman %	Mean value of AHF % 0–20	21–40	41–64	≥65
0–10	8	19	42	24
11–19	3	8	12	14
≥20	1	8	33	62

Table 39

Correlation beetween bleeding time according to Duke and Ivy and platelet adhesiveness according to Salzman (cases with bleeding time according to Duke of less than 30′ bleeding time according to Ivy not determined, not included).

Mean value (%) of platelet adhesiveness according to Salzman	Mean values of bleeding time according to Duke >30′	Duke <30′ Ivy >30′	Ivy 16–30′	Ivy ≤15′[1])
0–10	11	28	36	20
11–19	4	8	13	12
≥20	1	6	31	67

[1]) in Stockholm ≤ 12′

Statistical calculation was also made with rank correlation. Mean values for AHF and for platelet adhesiveness according to Salzman were ranked from lowest to highest values. Mean values for bleeding time were ranked as follows: Cases of bleeding time according to Duke >30 minutes, cases of bleeding time according to Duke <30 minutes, according to Ivy >30 minutes and finally values of bleeding time according to Ivy <30 minutes arranged in a descending scale. The results of rank correlations are given in Table 40.

Table 40

Rank correlations

	R	r	Number of pairs
AHF/bleeding time	0.65	0.67	427
AHF/platelet adhesiveness	0.35	0.36	227
Platelet adhesiveness/ /bleeding time	0.45	0.47	229

Here, the correlations were clearly positive ($p < 0.01$): with the highest coefficients for the correlations between AHF and bleeding time and lowest for the correlation between AHF and platelet adhesiveness according to Salzman.

Genetic investigations by us and by others (see page 87) have shown that the disease is inherited as an autosomal dominant. The investigations in our material of parents and children revealed a smaller number of affected persons than expected, especially if we consider only those cases where the disease had been diagnosed with certainty. It is therefore probable that most of the examined persons in whom the results obtained were "intermediate" are carriers of the gene but in whom the disease is of low expressivity and therefore has not become manifest.

In doubtful cases the diagnosis may be confirmed by administration of Fraction I–0 or fresh plasma and estimation of the effect on the AHF and bleeding time, which react in a characteristic way in von Willebrand's disease (see page 7). This method was used mainly on probands in our investigation.

General considerations

In severe cases of von Willebrand's disease the diagnosis is not difficult if facilities of a special laboratory are available. Besides a pronounced bleeding tendency in these cases the AHF is much decreased and the bleeding time by the method of Duke and by the method of Ivy is markedly prolonged.

Most of our patients, however, had mild von Willebrand's disease. Here the AHF-values were generally slightly or moderately decreased, while the bleeding time was prolonged according to Ivy but often normal according to Duke. In the mildest cases the bleeding tendency was barely noticeable or had not been noticed by the patient. The bleeding time according to the method of Duke in such cases is usually normal, and the AHF and bleeding time according to Ivy approach the limits of the normal ranges.

In a fairly large number of the persons examined, especially in relatives of the probands, certain findings were normal, while others suggested the presence of the disease in a mild form. Evaluation of such cases is made still more difficult by the above mentioned variation in the results of the tests which may be due partly to sources of error of the method and partly to a variation in the severity of the disease. It is therefore always necessary to obtain samples again and to repeat the tests to decide whether the disease is present or not, and such a decision may even then sometimes be difficult. In doubtful cases we classified the results as "intermediate".

Differential diagnosis of von Willebrand's disease

In patients with obvious bleeding tendency [illegible] disease it is often necessary to differentiate [illegible] von Willebrand's disease, mild haemophilia A, [illegible] asthenia and different types of [illegible] function.

The simplest method for distinguishing [illegible] philia A from von Willebrand's disease [illegible] of the bleeding time according to Ivy [illegible] philia is normal. In those cases of [illegible] disease which have AHF [illegible] seen in mild haemophilia [illegible] to Ivy is practically always [illegible] cases with borderline values for the Ivy bleeding time the decision may however [illegible] Family investigations [illegible] tion. Determination of [illegible] to Salzman may also be [illegible] of the differential [illegible] for differentiating the [illegible] Fraction I–0 and [illegible] by the AHF [illegible] repeatedly for at least one day.

Difficulties [illegible] between von Willebrand's disease and [illegible] lia are [illegible] (see Tables 41 and [illegible]

Table 41

Family 57

Case	Sex	Born	Type	Bleeding history N	O	TS	TO	T	E	GI	UT	M	Part	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Examinations Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III 2 KÅA	M	1919	M	2				3							1		2	2		2			9/63	3 7	>30	10		
																							9/63	4 5	3	11		
																							8/64	5 2	3	31		
																							10/68	4 4	30		13	
																							11/69	3 3	10	10	12	before inf
																							Inf of 200 ml F I–0					
																												After inf.
																								2 2	12	–		15 min.
																							–			77		3 hours
																										27		6
																									10	19	31	24
																										13		28
																									10	10		48
																										14		52
																										11		72
II 4 OB	M	1898	M														2			2								
III 1 EE	M	1915	M1	1																2			6/66	2	2	14	24	
III 3 TT	M	1921	M1												1		1		1m2	2			11/67	2	1	33		
																									[illegible]			
III 13 KTR	M	1948	M1														1			1	To 3							
III 15 JER	M	1957	MI				2										2						1/68			70		
V 3 AN	M	1964	MI	2											1					2	Trach 3		6/67	1	16			
																							10/68		10	70	40	
V 4 PL	M	1964	MI												1								10/68	1	8	4	62	
II 2 AB	F	1893	Carrier	1						2	1	1			1					2			10/68	2	8	75*	21	
IV 1 IN	F	1942	Carrier									1	1		1			1		1			10/68	4	10	45*	39	
IV 3 ML	F	1948	Carrier	1																1			11/67	1	10	50*	7	
																							10/68			38*	24	
V 2 SN	F	1963	Carrier												1								10/68			29*		
II 1 EA	M	1887	N																				6/67	1 2	9	75		
III 4 HB	M	1924	N																				11/67	4 3	14	85	55	
IV 2 PEE	M	1961	N																				8/65	2	5	128		
IV 4 MG	F	1945	N																				2/65		8	71		pregnant
IV 7 LÅA	M	1951	N																				8/64	2 3	18	125		
IV 8 BOA	M	1956	N	1																			8/64	3 2	14	107		
IV 9 JOA	M	1959	N																				8/64	2 3	12	69		
V 1 TN	M	1962	N																				10/68	3 3	12	107*		

Table 42

Family 63

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sem.	Date m/year	Duke min.	Ivy min.	AHF %	Sx ⁄	Remarks
IV 16 UÖ	M	1937	Ml	1	1										1		2			2			3/63	*18*	>*30*	*13*		
																							6/67	2 3	*19*	*35*	22	
																							10/68	5 5	>*30*	*19*	24	
																							11/70	3	*17*	*18*		'6 before inf
																							Inf. of 200 ml F I–0					After inf
																							–	3	*22*	'6		15 min.
																									'0	*27*		2 hours
																									'0	'6		5
																							–	2	*18*	*23*	36	24 –
																									'0	*18*		28
																									13	*15*		48 –
II-2 NO	M	1861	Mı														1			3								
III.14 JO	M	1910	Ml														1			1			6/43	2				Coag time 35 min.
III.21 AM	M	1922	Ml														1			3								
IV.2 BJ	M	1932	Mı														1			3				3		*11*		
IV 6 BJ	M	1938	M																				6/67	1 1	'8	*35*		
IV 17 LÖ	M	1940	Ml	1													1						6/67	1 2	>30	*19*		
IV 19 KÖ	M	1952	Ml	1			3										1			1			6,67	4 8	>30	40	47	
III 19 FÖ	F	1914	Carrier	1								1			1		1			2			10/68	2 3	15	*23*	26	
III.18 HÖ	M	1913	N																				6/67	3 2	*17*	85		

Also among Swedish patients gastro-intestinal bleeding was the commonest cause of death. In one case (34 III.3 IL) the issue of such bleeding was fatal though specific treatment had been given. The quantities of available Fraction I–O proved insufficient. As elsewhere mentioned (page 129), gastro-intestinal bleeding also in patients without a bleeding disease is often serious and claims a high mortality.

Deaths from intracranial haemorrhage have occurred in three of our patients and in all of them after trauma. Two of them had a firm diagnosis of severe von Willebrand's disease (4 IV 1 GB and 13 III.3 JIE). For various reasons prophylactic treatment had not been given.

Haemoptysis with a fatal outcome had occurred in two relatives of 17 IV.5 LL. Both of them had died many years ago.

Four patients with von Willebrand's disease have died from bleeding after operation, including two after subtotal gastrectomy. In none of these 4 cases was the disease diagnosed praeoperatively and no prophylaxis had been given.

Bleedings, severely affecting working capacity have been uncommon among our patients.

One patient (11 II.1 GB) has for several years had gastric bleedings, which have recurred so often that he gradually became disabled and was granted a sick pension.

Some women (21 III.3 MÅ, 27 III 4 KR, 60 II 10 ES, 73 II:5 SE and 50 I.2 MA) have had severely anaemising menorrhagia for several years. Three women (1 V.5 BT, 4 IV 1 GB and 16 III 1 AKZ) were subjected to hysterectomy or roentgen castration soon after menarche because of severe vaginal bleeding.

In three patients with severe von Willebrand's disease (8 II.1 RB, 9 III.1 ES and 27 III 4 KR) joint bleeding caused considerable impairment of function of some joints. All three patients can, however, walk and are socially well adapted and working as a dental technician, office clerk, and housewife, respectively.

Otherwise our patients have been able to lead a largely ordinary life despite occasional severe bleeding symptoms.

Risk of von Willebrand's disease among offspring of affected patients

A question of particular interest for many patients with von Willebrand's disease is the risk of affection of offspring. The literature furnishes no answer to this question.

With an autosomal dominant mode of inheritance the predisposition (gene) should be transmitted to 50 % of children of persons affected with the disease, but, judging from the penetrance of the condition found among the parents (page 83), the risk of the children being affected is somewhat lower, about 40 %. And judging from the examination of children of the probands (page 83), the risk should be still lower.

About one eighth of the patients in our material had the severe form of the disease [1]). This form was probably over represented in the material because patients with this type seek medical advice much more often than those with only mild symptoms. It would thus appear that the risk of a child of a patient with von Willebrand's disease being affected with the severe form of the disease is less than one eighth of 40%, that is less than 5%.

An AHF-dependence of affected children on affected parents was demonstrated among Swedish patients with von Willebrand's disease with a significance of $p < 0.05$ (page 84). But all of our patients with the severe form of the disease were offspring of parents with the mild form of the condition. Only 5 of those with the severe form of the disease have themselves given birth (all together 6 children). The children are still so young that they have not yet been examined with comprehensive laboratory tests. But in two of them the Duke bleeding time has been measured and has proved normal. None of the 6 children have so far shown clinical sign of bleeding tendency.

As far as AHF is concerned in our series, siblings resembled one another more closely than unrelated patients (page 83). Three probands with severe von Willebrand's disease (2 III.2 YL, 4 IV.1 GB and 13 III.2 SE) had investigated siblings who also had the severe form of the condition. Only one patient with severe von Willebrand's disease (23 II 4 SW) had a sibling with the mild form of the disease.

According to the calculations above, the risk of the *bleeding disease among offspring of affected parents* could thus be estimated at about 40 %. The risk of a child developing the severe form of the condition is much smaller, probably less than 5 %. In the estimation of the risk, knowledge of the form of the condition, *i.e.* severe or mild, of the parent appears to be of little value. However, *if one child is severely ill* the risk of later siblings also developing the severe form of the disease appears considerable.

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1) calculated on patients with a firm diagnosis of von Willebrand's disease, including those who had died before 1/1 1968.

THERAPY AND PROPHYLAXIS

Formerly treatment of bleeding in von Willebrand's disease consisted of local measures to arrest the bleeding and blood transfusions to compensate for the blood loss. Such local measures consisted of, for example, cauterisation with chromic acid for nosebleeding, suturing of bleeding wounds and application of thrombin-saturated material to the surface of bleeding wounds.

TREATMENT WITH PLASMA AND PLASMA FRACTIONS

In the latter half of the 1950s Nilsson, Blombäck and co-workers found Fraction I–0 (F I-0) from normal fresh plasma to contain a factor, the so-called von Willebrand-factor, which stimulates the production of AHF and shortens the bleeding time in von Willebrand's disease (see page 7–8 – historical). *F I-0* contains also AHF and fibrinogen. The von Willebrand-factor occurs also in fresh and in deep-frozen plasma, but in lower concentration than in F I-O.

Treatment with fresh plasma and F I–O has since been tried not only in Sweden (see below), but also abroad.

Good results of theraphy and prophylaxis with fresh plasma for bleeding in von Willebrand's disease have been reported by *e.g.* Ponka, Monto and Welborn (1967) Mathers and Castner (1967) and Hill and Taylor (1968). In the severe form of von Willebrand disease fresh plasma has, however, most often proved insufficient to arrest or prevent bleeding, *e.g.* at operation or delivery (Arrants, Jordan & Newcomb 196_, Walker & Dormandy 1968). In cases with a severe bleeding tendency satisfactory haemostasis requires considerable amounts of plasma, which may create circulatory problems (Henrion 1965, Cornu 1965, Rizza & Biggs 1969).

F I-O has been used in other countries mainly in association with surgery and mostly with success (Weiss 1962, Biggs & Mathews 1963, Sherlock 1964 and Castaldi et al. 1967). Less good results have been reported by Brandstetter et al. (1968) in the treatment of patient after operation because of gastric bleeding and by Salomon and Tatarski (1965) in association with treatment of spontaneous gastrointestinal bleeding. – Cornu (1965) and Henrion (1965) stress the difficulty encountered in the production of F I-O preparations of good quality.

In recent years patients with von Willebrand's disease have often been treated with Pool's cryoprecipitate (see page 9) and good effects of such treatment have been reported by Bennet and Dormandy (1966) Castaldi et al. (1967), Abildgaard et al. (1968), Rizza and Biggs (1969), Komp, Nolan and Carpenter (1970) and others.

PRESENT SERIES

Since 1956 many Swedish patients with von Willebrand's disease have been treated with F I–O and/or fresh plasma in the event of acute bleeding and prophylactically at delivery and operations. F I-O has been given mainly to patients with the severe form of von Willebrand's disease, but in cases of severe bleeding or at major operations also to patients with the mild form of von Willebrand's disease. Patients with the mild form of the disease are otherwise often treated with fresh plasma. Occasionally prophylaxis or treatment with fresh blood has been tried, which is otherwise used for compensating blood loss.

Prophylaxis with F I–0 and fresh plasma at operations

Major operations

Seventeen of the patients in the present material have undergone all together 20 major operations under protection of F I-0 or fresh plasma or both (Table 44). 8 of the operations were performed on patients with the severe form of von Willebrand's disease.

Thirteen operations, including 4 on patients with severe von Willebrand's disease, could be performed without any abnormal loss of blood. The AHF at operation in these cases was between 50 and 115% and during the first week after operation it was maintained at levels above 40%. At operation the bleeding time had been normal according to Duke (⩽5 minutes), but during treatment after operation it sometimes varied considerably between normal and more than 30 minutes.

In one patient (16 III.1 AKZ) with severe von Willebrand's disease hysterectomy because of life-

Table 44

M jor operations performed under protection of F I – 0 and/or fresh plasma

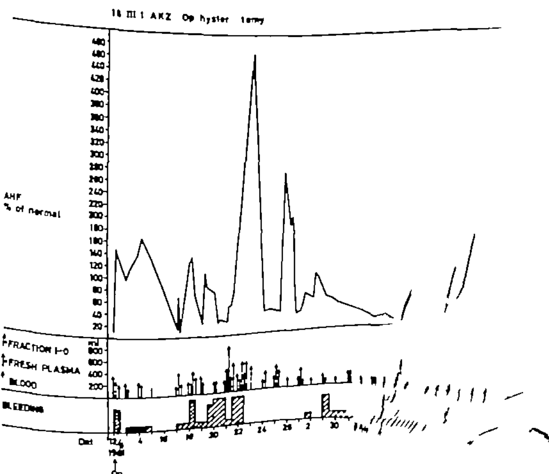
Patient	Age years	Type	Operation	Given postoperatively F I-0 x 100 ml	Given postoperatively Plasma 400 ml	Given praeoperatively F I-0 x 100 ml	Given praeoperatively Plasma x 400 ml	Blood x 450 ml	Dur of treatm. days	Comments
23 III 12 KW	10	S	Tonsillectomy	4		16			13	
1 V 5 BT	28	S	Ventriculotomy	5		56			22	
103 I 1 WW	44	Mi	Gastrectomy	2		8			6	
18 III 1 VA	45	Mi	Cholecystectomy	3	1	11 1/2	4	4 1/2	5	3rd – 4 th day after op. fairly profuse bleeding in op. wound
27 III 4 KR	48	S	Cholecystectomy + Choledocholithotomy	5		51		1	21	Diffuse bleeding in op.-field duri g op.
28 II 4 AS	49	Mi	Cholecystectomy	5		25 1/2	9 1/2	1	38	
III 2 IN	28	Ml		2		2			2	
101 III MO	39	M		3	1 1/2				2	
31 II 4 LJ	57	M	Choledocholithotomy	2		2			5	
11 III OB	57	Sv	Expl. laparotomy + expl gastrotomy and enterotomy + pyloroplasty + vagotomy	11		174		6	36	On the 4th – 8th day after operation bleeding time accordi g to Duke p to more than 30 min. and profuse bleeding from intestine and oozing from op.-wound.
11 II 1 OB	57	Sv	Expl. laporatomy + lysis of the small intestine	4		33			21	
1 V.5 BT	16	S	Hysterectomy	3		10			43	At vaginal palpation 19 days after op. vaginal rupture and profuse bleeding.
16 III 1 AKZ	15	S	Hysterectomy	3 1/2		104		11	35	Treatment with F I-0 discontinued after 3 days. From 6th day after op. profuse bleeding, which later conti- ued despite treatment with F I-0 and fresh plasma. Signs of anticoagulants.
21 III.3 MÅ	21	Ml		2		1			3	Postoperative infiltrates in op.-region
42 III.19 IH	50	Ml		4		11		4	12	Bleeding at op., 2 blood transfusions given. Treatment with F I-0 disconti- nued after 2 days. 5 days later profuse vaginal bleeding. Further 2 blood transfusions given.
2 III.2 YL	28	Sv	Salpingo-oophorectomy	2	2	37	28	2	27	At. op. numerous adhesions. Profuse bleeding at op. and one week later Pat. received 1 + 1 blood transfusions.
43 IV 4 EJ	53	Ml			2		5		7	
73 II.5 SE	41	Ml	Oophorectomy	1 1/2	2	10	6		14	
60 II 10 ES	35	Ml	Op. of astrocytoma		10		13		14	Postoperative orbital blood effusion.
70 IL KH	26	Ml	Ablatio mammae		1		4	2	5	Local bleeding during the first few days after op. Hb decreased from 12.7 to 9 7 g/100 ml.

threatening menorrhagia was attended by serious haemorrhagic complications. She was operated upon under protection of large doses of F I-O but the treatment was discontinued already 3 days after the operation (Fig 6) The AHF then fell (lowest level 10 %), and on 6th day the patient bled heavily from the wound. She occasionally bled profusely during the following weeks despite repeated doses of F I-O The AHF-level fluctuated considerably Not until 7 weeks after the operation could the patient be discharged in a good condition. Examinations showed signs of anticoagulants during treatment as well as several years later

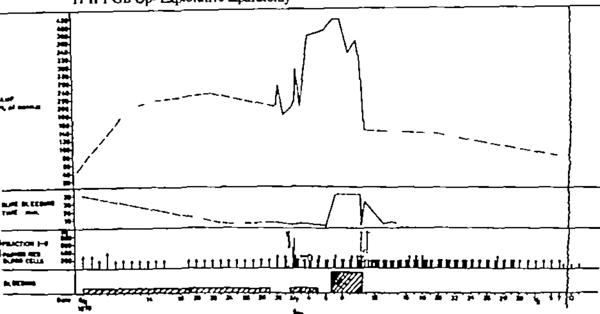
Another patient, 11 III.1 GB, who likewise had the severe form of Willebrand's disease, had for many years had disabling gastro-intestinal bleeding. He was finally subjected to explorative abdominal surgery under protection of F I-O He was in a poor general condition because of narcomania and was found to have hypoproteinaemia with a serum protein concentration down to 4.3 g/100 ml The AHF level during treatment reached high levels, over 400 (Fig 7) The first few days the bleeding time was normal, and no increased bleeding was noted at the operation or soon afterwards. On the 4th to 8th day after the operation, however the bleeding time according to Duke was prolonged to more than 30 minutes, though the patient received continued treatment. He then bled from the intestine and there was some oozing from the operation wound. Treatment with F I – O was intensified further the bleeding time became normal, the bleeding stopped and did not recur

A somewhat increased bleeding tendency was observed in two further patients with severe von Willebrand's disease (2 III.2 YL and 27 III 4 KR) ... had been subjected to salpingo-oophorectomy ...

Fig 6



11 II 1 GB Op- Explorative laparatomy



cholecystectomy + choledocholithotomy respectively under protection of F I–O and fresh plasma.

Moderate bleeding complications despite prophyl-is occurred also in three patients with mild von illebrand's disease. The operations performed were lecystectomy (18 II.1 VÅ), hysterectomy (42 III.19 IH) and ablatio mammae (70 II.1 KH). After hysterectomy in 42 III.19 IH the prophylactic treatment was stopped early two days after operation, and 5 days later the patient bled rather profusely from the vagina. In 70 II 1 KH ablatio mammae was performed under protection of fresh plasma alone.

Minor operations

Fourteen patients had undergone all together 18 minor operations under protection of F I-O and/or fresh plasma (Table 45). Five of the patients had severe von Willebrand's disease. Profuse bleeding occurred in 19 III.1 SA, who was subjected to legal abortion with exaeresis instrumentalis. Judging from the laboratory values, she had mild von Willebrand's disease (mean AHF 60 %, bleeding time according to Duke 5 minutes and according to Ivy on the average, 23 minutes) but she had previously had suggestive, heavy uterine bleedings. Treatment was performed under protection of fresh plasma only

In the remaining 17 cases minor operations had not been accompanied by any abnormal bleeding.

Tooth extractions

Tooth extraction is a relatively minor operation, but has been shown to carry a considerable risk of bleeding (page 100). Prophylaxis with fresh blood alone was tried in 4 of our cases (7 III.1 MA, 13 III.2 SE, 20 III.2 KGP and 75 II.1 BT) but proved insufficient to prevent bleeding in the last three. In one (13 III.2 SE) of the cases the bleeding was very profuse.

F I-O and/or fresh plasma was given prophylactically to 40 of the Swedish patients before and after extraction of teeth on all together 68 occasions (see Table 46). During operation and the first few days afterwards the AHF-level was usually between 30 and 80 %. The bleeding time according to Duke was on the day of the operation mostly less than 10 minutes, but often rose to more than 30 minutes before the specific treatment was withdrawn.

On most occasions tooth extraction was not complicated by abnormal bleeding

On 8 of the 68 occasions bleeding was profuse, despite the prophylactic treatment given

In two (4 IV 1 GB and 100 III:4 AS) of these cases the specific treatment was discontinued early and bleedings occurred some days later — about a week after the operation. Two other patients (1 V:5

Table 45

Minor operations performed under protection of F I 0 and/or fresh plasma

Patient			Age years	Type	Operation	Given preoperatively F I-0 100 ml	Given preoperatively Plasma x 400 ml	Given postoperatively F I-0 x 100 ml	Given postoperatively Plasma 400 ml	Given postoperatively Blood 450 ml	Dur. of treatm. days	Comments
33	III 2	AR	20	Sv	Removal of tartar	2,5		2			1 + 1	Op. in 2 sittings
29	III.1	IOK	41	Mi	Stapedectomy	2		2			2	
77	II.7	HR	23	Ml	Appendectomy				9		6	
81	II 3	NF	64	Mi		2		5			5	
75	II 1	BT	38	M	Op. of inguinal hernia	2		3			3	
		BT	40	Mi		2		3			3	
42	III.28	KE	30	Mi	Conisation	2		1			2	
		KB	30	M	Sterilisation + appendectomy	2		4			3	
19	II.1	SA	4	Mi	Exstirpation uteri		1		8	5	15	Bleeding from vagina during 2 weeks after op. Hb down to 10 6 g/100 ml.
29	III.1	IOK	39	M	Tracheotomy	1						
28	II.4	AS	53	Mi	Lymph node biopsy	1					1	
75	II 1	BT	38	M	Meatotomy			2			2	
3	III:4	EK	72	Sv	Extirpation of skin tumour		1,5		3		3	After the last plasma infusion allergical lid oedema.
9	III.1	ES	23	Sv		5	1 (+ 450 ml (blood)	5	2		5	
29	III.1	IOK	39	Ml	Skin transplantation	1						
10	III.1	MCA	25	Sv	Pleural puncture	1		2				
5	III:5	PP	49	Ml	Myelography	2					2	
27	III-4	KR	43	Sv	Joint puncture	2		1	3		1 2	

Table 48

Acute bleedings treated with F I-0 and/or fresh plasma

Patient			Age years	Type	Symptom	F I-0 100 ml	Given Plasma 400 ml	Blood x450 ml	Dur of treatm. days	Comments
12	IV 2	KPA	9	S	Nose bleeding	2		3		
16	III 1	AKZ	16	S	Nose bleeding	17			15	Simultaneous ovarian bleeding
		AKX	19	Sv		1		1	1	
22	II 1	ID	24	Sv	Nose bleeding	10	10	10	9	Bleeding after stopping treatment with "p-pills
30	III 2	AW	8	MI	Nose bleeding	2			4	
42	IV 62	PS		MI	Nose bleeding	1			1	
61	III 1	EK	7	MI	Nose bleeding		0,5		1	Cauterised with chromic acid
90	III 1	ML	1	Sv	Nose bleeding	0,5			1	
		ML	1	S		0,5			1	
		ML	2	Sv		1			1	
		ML	3	S		0,5		1	1	
92	III 1	AM	1	Sv	Nose bleeding				1	Cauterised with chromic acid
		AM	1	S			0,5	0,5	1	
3	III 1	MH	18	Sv	Gingival bleeding		+			
		MH	21	Sv			+			
6	IV 2	RF	6	Sv	Bleeding at tooth shedding	1			1	
40	III 3	AMW	7	Sv	Bleeding at tooth shedding	1			1	
		AMW	11	Sv			1		1	
		AMW	11	Sv		1	1		2	
		AMW	11	Sv		1	1		3	
		AMW	11	S			1,5	1	3	
6	IV.2	RF	2	S	Traumatic oral bleeding		0,5	2	3	
90	III 1	ML	1	Sv	Traumatic oral bleeding	0,5			1	
100	III 4	AS	4	MI	Traumatic oral bleeding	3			11	
103	II.3	AW	7	Sv	Traumatic oral bleeding	1			1	Pat. received also ε-ACA
2	III.3	GL	7	S	Tonsillar bleeding	1,5			1	
9	III 1	ES	29	S	Tonsillar bleeding		3			
23	III.12	KW	8	Sv	Tonsillar bleeding	2		2	1	
		KW	10	Sv		2		2	1	
40	III.3	AMW	10	Sv	Tonsillar bleeding	1		1	1	
6	IV.2	RF	1	Sv	Bleeding after venous puncture	1			1	
92	III-1	AM	1	S	Bleeding after arterial puncture	1,5				
6	IV.2	RF	13	Sv	Subcutaneous bleeding		3,5		5	
40	III 3	AMW	8	Sv	Subcutaneous bleeding	1	0,5		1+1	
16	III.1	AKZ	12	Sv	Bleeding in floor of mouth	10			10	
6	IV.2	RF	12	Sv	Intramuscular bleeding	2			4	

Table 43 (continued)

Acute bleedings treated with F I-0 and/or fresh plasma

Patient			Age years	Type	Symptom	F I-0 100 ml	Given Plasma 400 ml	Blood 450 ml	Du of treat. days	Comments
63	II:5	GL	86	MI	Intramuscular bleeding		10		10	
42	IV:46	ME	10	MI	Traumatic bleeding	2			3	
48	III 1	BH	7	S	Traumatic bleeding	2		0,5	2	
1	V.5	BT	28	S	Gastrointestinal bleeding	31		23	30	Bleeding from gastric polyp
9	III 1	ES	23	Sv	Gastrointestinal bleeding		3	2		
10	III 1	MCA	32	Sv	Gastrointestinal bleeding	5	2	6	4	
		MCA	34	S		19		1	15	
		MCA	36	Sv		4			4	
11	II:1	GB	51 56	S	Gastrointestinal bleeding	>300		numerous		More than 100 periods of treatment
34	III 2	IL	45	M	Gastrointestinal bleeding	3		several	3	Patient died before further F I-0 could be obtained
50	I 2	MA	41	Mi	Gastrointestinal bleeding	2				
89	II 2	HN	81	Mi	Gastrointestinal bleeding	2	10	2	2	Hepatitis afterwards
7	III 1	MA	25	Sv	Haematuria		8		7	
13	III.2	SE	23	Sv	Haematuria	2	3		1	
		SE	23	S			1	1	2	
		SE	24	Sv			1		1	
		SE	24	Sv			7		5	
		SE	26	Sv			3		2	
2	III 3	GL	12	Sv	Menorrhagia	1		2	2	
		GL	14	Sv		1		3		
		GL	15	Sv		2		3		
16	III.1	AKZ	12	Sv	Menorrhagia		4	2	8	Bleeding stopped after treatment with progesterone
23	III.12	KW	13	S	Menorrhagia	1		2	1	Pat received also ε ACA
42	III.19	IH	50	Mi	Menorrhagia	2			1	
54	III.2	PD	12	Mi	Menorrhagia		1		1	
7	III.1	MA	14	Sv	Ovarian bleeding	1			1	
10	III.1	MCA	28	Sv	Ovarian bleeding	2		3	3	
		MCA	35	Sv		8			8	Pat received also ε ACA
16	III.1	AKZ	16	Sv	Ovarian bleeding	17			15	Simultaneous nose bleeding
6	IV.2	RF	8	S	Joint bleeding	2	2		6	
6	IV.2	RF	8	S	Joint bleeding	2	2		6	
		RF	12	S			1		1	
8	II.1	RB	33	Sv	Joint bleeding		1		1	
		RB	33	S			1		1	
		RB	34	S			1		1	
		RB	34	Sv			1		1	

Table 49 (continued)

Acute bleedings treated with F I-0 and/or fresh plasma

Patient			Age years	Type	Symptom	F I-0 x100 ml	Given Plasma 400 ml	Blood x450 ml	Dur. of treatm. days	Comments
8	III I	RB	34	S	Joint bleeding		1		1	
		RB	34	S			1		1	
		RB	34	S			4			
		RB	34	S		1			1	
		RB	35	S			2,5			
		RB	35	Sv			1		1	–
9	III I	ES	20	S	Joint bleeding		1		1	
		ES	21	S			1		1	
		ES	21	S			2			
		ES	22	Sv			1		1	
		ES	23	Sv			1		1	
		ES	23	S			1		1	
		ES	23	S			1		1	
		ES	23	S			2			
1	IV I	AJ	3	S	Joint bleeding		0,5		1	
40	III 3	AMW	7	S	Joi t bleeding		1		1	
		AMW	8	S			1		1	
		AMW	8	Sv			1		1	
		AMW	8	Sv			1		1	
		AMW	8	S			2		2	
48	III I	BH	5	Sv	Joint bleeding		3		4	
		BH	7	Sv			2		3	
		BH	7	Sv			1		1	
		BH	7	Sv			1		1	Hepatitis afterwards
		BH	7	Sv			2		5	
		BH	7	S			1		1	
		BH	7	Sv			1		1	
		BH	8	Sv			2		5	
100	III.4	AS	4	Mi	Joint bleeding	1			1	
	III:6	JN	3	Mi	Joint bleeding		0,25		1	
42	III.33	BAA	28	Mi	Eye bleeding		5		5	
92	III.1	AM	1	S	Retroperitoneal bleeding?	1			1	
50	I.2	MA	41	Mi	Postextraction haemorrhage	1			1	Hepatitis afterwards
111	II.2	TE	5	Mi	Postextraction haemorrhage	15			11	
73	II.5	SE	38	Mi	Bleeding after hysterectomy	52,5	30	50	22[1])	Bleeding did not stop until after surgical operations.
88	II:2	IH	49	Mi	Bleeding after hysterectomy	2	9	9	45[1])	

[1]) Duration from the beginning of treatment with plasma.

Fig 10

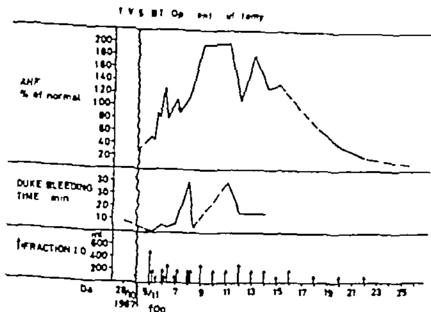


Fig 11

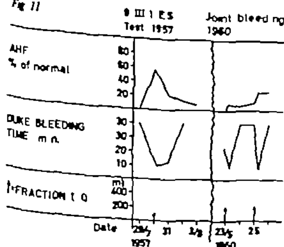
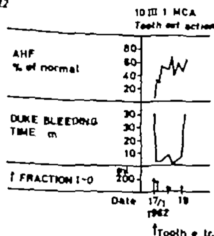


Fig 12



Present series

In Swedish patients given F I-O or fresh plasma the AHF level and the bleeding time were often followed with repeated determinations. The results are illustrated *by fig. 6–18 (page 1 1–135).*

With but few exceptions such treatment raised the AHF in the patient's blood. The highest values were *generally obtained 6–8 hours after* infusion, and the *AHF-level was then higher than could be expected* from the amount of AHF given. The increase was larger than that obtained on infusion of a corresponding amount to patients with haemophilia A. The effect *of a dose usually lasted for 24–28 hours.* When the doses were given at 24 hour or shorter intervals, they generally produced a stepped elevation of the AHF level, and sometimes the AHF-values exceeded 100 even in patients with previously very low values

Fig 13

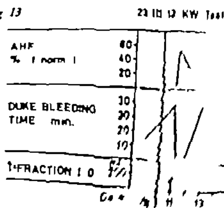


Fig 14

27 III 4 KR Cholecystectomy

AHF
% of normal
280
240
220
200
180
160
140
120
100
80
60
40
20

DUKE BLEEDING
TIME min
>30
30
20
10

ml
FRACTION I-O
BLOOD
600
400
200

BLEEDING

Date 15/9 17 19 21 23 25 27 29 1/10 3 5 7 9
1960
Op

Fig 15

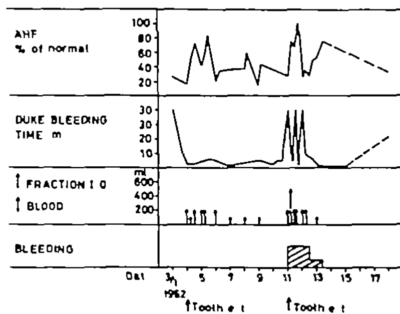
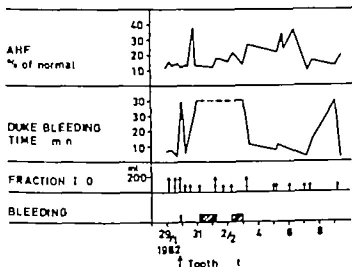


Fig 16



(Figs 7 10 and 14). After repeated administration of F I–0 for a long period the effect sometimes became less certain and brief (Figs. 6, 8 and 14). In one of these cases (Fig. 6, 16 III 1 AKZ) examination has revealed signs of a circulating anticoagulant.

An unsatisfaying response by AHF from the very beginning was seen in 35 II:5 PT (Fig. 16) and was found to be due to an anticoagulant. In some patients (28 II:4 AS Fig. 15 and 33 III.2 AR) the response was poor when F I–0 had been prepared in large batches with freshly frozen plasma as a basic material and when the fractions had been sterile filtered before use (see page 12 Material and methods).

The effect of F I–0 and fresh plasma on Duke's bleeding time was good in most cases but generally shorter than the effect on the AHF level (see page 7). When the doses used were too small and given only at intervals of more than 12 hours the bleeding time in patients with severe von Willebrand's disease often was abnormally long in spite of treatment (Figs 7 8 9 14 and 15). With the comercially available preparations of F I–0 in recent years the effect on the bleeding time has sometimes been less satisfactory (45 III 1 RO 103 II.3 AW Fig 18)

Fig 17

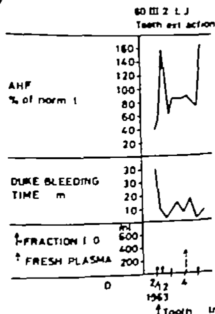
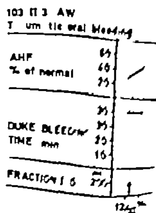


Fig 18



Ivy bleeding time was barely affected by the treatment. This may be due at least partly to the fact that the bleeding time was not measured for more than 30 minutes and that a reduction of a markedly prolonged bleeding time might have not been noticed

The results of treatment on the patient's bleeding tendency usually varied with the effect of treatment on the AHF level and Duke bleeding time. When the bleeding time according to Duke was markedly prolonged, profuse bleeding sometimes occurred even when the AHF-level was high (Figs. 7 8 and 9).

A normal bleeding time according to Duke usually reflected good control of the bleeding tendency also at major operations even when the bleeding time according to Ivy was still prolonged.

The profuse bleeding that occasionally occurred during treatment usually occurred when treatment was tentatively withdrawn or when F I-O or plasma was given at longer intervals.

In some cases determinations were made of platelet adhesiveness according to Salzman before and after administration of F I−0. The results are listed in Table 49

Side effects

The most serious and most common complication of treatment with F I-O and plasma was serum hepatitis. It occurred in 6 cases: 8 II 1 RB, 13 III.2 SE, 16 III.1 AKZ, 48 III 1 BH, 50 I.2 MA and 89 II.2 HN. It was most severe in 50 I.2 MA in whom the bilirubin rose to 5 1 mg/100 ml, GPT to 2,000 U and Thymol ext. to max 0 64 (normal $<$0 10) Liver function gradually became normal within some months. — In the other cases the symptoms of hepatitis were relatively mild and brief

Signs of a circulating anticoagulant were seen in two patients: 16 III.1 AKZ and 35 II 4 PT The former had previously been repeatedly treated with F I-O and fresh plasma. In 35 II 4 PT on the other hand, the very first dose of F I-O had a poor effect on the AHF-level. On electrophoresis a band was found in the β_2-globulin fraction. A connection between the band and the anti-AHF is possible Later the patient fell ill with myeloma.

In three cases (36 IV.2 IN 38 IV·4 KS and 75 II.1 BT) treatment with fresh plasma was followed by aller

Table 49

Platelet adhesiveness according to Salzman before and after administration of F I−0

	Platelet-adhesiveness		Bleeding time according to Duke		
…tient	before infusion of F I-0[1])	after infusion of F I-0[1])	before infusion of F I-0[1])	after infusion of F I-0[1])	Time after infusion of F I-0[1])
IV 5 BT	7				
	10	11,5	> 30	3	
10 III 1 MCA	0	8	> 30	8	20′
11 II 1 GB	*3*	6	> 30		0′
	3	3		8	
	3	8		5′30″	
	3	3		2	
12 III 2 KPA	6	2	20	11	20′
		4			20′
		7			20′
		2		4′30′	20′
103 I 1 WW	0	24			
II.3 AW	20	22			
?7 IV 1 KR	17	10			24 hr's

[1]) dose 100 900 ml

Treatment thus had no regular or particular effect on platelet adhesiveness. No normalisation occurred parallel to the bleeding time according to Duke

pe urticaria and oedema. In 38 IV 4 KS there was also a swelling of the throat and in 75 III 1 BT hoarseness. But in none of the patients were the symptoms serious.

TREATMENT WITH ∈ ACA and AMCA

Therapy and prophylaxis with ∈-ACA have been used by some investigators in recent years. Good results have been reported by Henrion and Corno (1964). Bowes (1969) and van Creveld and Schellekens (1969), on the other hand, found such drugs to have no effect on the bleeding tendency.

Present series

Data on therapy or prophylaxis with ∈ ACA or AMCA are available for 20 patients with von Willebrand's disease in Sweden. ∈-ACA has been given i.v. in a dose of 12–45 g/24 hours or orally in a dose of 3 gx4–6. AMCA has been given in a dose of 1–4 g a day. The doses have been varied according to the patient's weight, the extent of operations, and the severity of the bleedings for which treatment was started.

It is difficult to assess the effect of medication because, as a rule, the patients had also received other treatment. One patient, 8 III 1 RB, with a strong predisposition to joint bleedings, however, reported a considerable improvement during almost 2 years' continous treatment with AMCA without any simultaneous therapy. During this period he has not had any recurrence of joint bleedings. At 34 years (1969) 13 III.2 SE was treated with AMCA became of obstinate nose-bleeding. The bleeding stopped after 6 hours. The patient previously had frequently recurrent bleeding from the urinary tract. He has since successfully used ∈ ACA or AMCA as soon as he has noticed signs of such bleeding and has not required hospitalisation. Some patients have tried daily treatment with AMCA at or before expected menstruation but have been unable to continue such treatment owing to side effects, especially in the form of abdominal pain and diarrhoea.

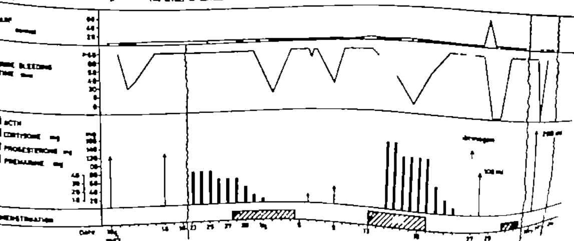
TREATMENT WITH CORTICOSTEROIDS AND ACTH

Cortisone has been recommended in the treatment of conditions with a normal platelet count and prolonged bleeding time, particularly by B. Jacobsson (1953 and 1957). In our series the effect of ACTH and cortisone was tried in 7 III 1 MA, who received treatment before and in association with profuse mentrual flow (Fig. 19). After treatment with ACTH and during treatment with cortisone the bleeding time transiently became shorter but not normal. During cortisone treatment the bleeding time again became prolonged before treatment was withdrawn. Therapy had no convincing effect on the menstrual flow.

TREATMENT WITH SEX HORMONES

Various sorts of hormone preparations have been tried in the treatment of menorrhagia in von Willebrand's disease during the last decades (Achenbach 1960, Carré et al. 1961, Barrow & Graham 1964a, Bonechi & Pasero 1964, Akman et al. 1965, Özoylu & Corbacioglu 1967 a and b, van Creveld & Shellekens 1969 and others).

Fig 19



In the 1960s contraceptives have become available in which oestrogenic and gestagenic components have been given usually in so called combined preparations. These preparations have been found to have a considerable depressive effect on menorrhagia (Carré et al. 1961 Henrion & Cornu 1964 Özsoylu & Corbacıoglu 1967 a and b, Walker & Dormandy 1968). The effect can probably be ascribed above all to the local effect of the hormones on the endometrium. But their possible effect on the coagulation mechanism and platelet adhesiveness has also been discussed and compared with the effect of pregnancy during which the AHF is also normally elevated.

Egeberg and Owren (1963) found that treatment with Enavid® (Searle) in a standard contraceptive dose to 4 healthy women caused an increase of the AHF which developed during the first and second week of treatment, while the values showed a tendency to return to the original levels soon after discontinuation of treatment.

Other investigators have not found oral contraceptives in ordinary doses to have any definite effect on the AHF (Rutherford et al. 1964, Brakman, Albrechtsen & Astrup 1967 Nilsson & Kullander 1967) However Nilsson and Kullander (1967) found the use of Anovlar® (Schering AG) in 4 times the ordinary dose for $2^1/_2-6$ months to raise the AHF by roughly 100%.

Özsoylu and Corbacioglu (1967 a and b) gave contraceptive pills to patients with von Willebrand's disease, even to men, and then followed the bleeding status with laboratory tests. They found the AHF to raise but not until treatment had been continued for 2–6 months and then not to reach a maximum until after 5–11 months. The male patients had by then developed gynaecomastia and in a few cases also behavioural disturbances. Platelet adhesiveness had not been affected by the hormone therapy and the bleeding time had not noticably improved.

Present series

One of our patients, a girl, 7 III 1 MA, was successfully treated in the middle of the 1950s with progesterone because of severe puberal menorrhage. Menorrhagia did not recur after withdrawal of the preparation after it had been used for one year. Progesterone therapy has since been used for similar symptoms in 2 III 3 GL and 16 III 1 AKZ. The former improved considerably while the effect of treatment on the latter was unsatisfactory. I this patient progesterone was therefore replaced by a testosterone preparation. After three years treatment the drug had had a strong virilising effect. Treatment was therefore discontinued and the patient was subjected to hysterectomy instead.

In recent years contraceptives with oestrogenic and gestagenic components, "p-pills" have been given to several Swedish patients because of menorrhagia, and the clinical results have been good. It appeared to be of interest to study the effect also on some of our patients regarding the AHF bleeding time according to Duke and Ivy and platelet adhesiveness.

Four women with von Willebrands disease of varying severity received pills Conlunette (Norethisteron 1 mg + Mestranol 0,1 mg) in a standard dose, *i.e.* one pill a day for three weeks followed by one week's pause. Treatment was continued for 3–5 months. The patients were examined before treatment, during treatment, during prescribed pauses in treatment and at least three weeks after the end of treatment. Three of the patients (38 IV 4 KS, 9 III 1 ES and 22 II 1 ID) had previously used similar "p-pills" and one of them (9 III 1 ES) did not wish to stop medication when the program had been concluded. The results are given in Table 50.

Treatment with "p-pills" thus had no noticeable effect on the values studied. The only remarkable finding was that all of the 4 patients studied had a lower mean AHF during the pauses in treatment than before, during and after treatment. Two, who had before treatment only had moderately increased bleeding time according to Duke showed a possible tendency to more prolonged bleeding time during the pauses.

During treatment with "p-pills" all the patients were free from menorrhagia, which had previously caused more or less severe symptoms. They also all reported that they felt better even regarding other bleeding symptoms which had before treatment often been troublesome such as tendency to nose-bleeding and bruising: 9 III 1 ES, who had formerly been regularly using "p-pills" stopped taking the pills for about one month before the present investigation. She had previously had troubles of joint bleeding, and during the pause symptoms of bleeding in the elbow knee and foot joint ocurred. 22 II 1 ID one month after she had stopped using the pills had severe nose-bleeding which resulted in shock necessitating several blood transfusions.

These bleeding symptoms thus occurred after discon-

Table 90

AHF bleeding time according to Duke and Ivy and platelet adhesiveness according to Salzman before, during and after treatment with "p-pills"

Patient	AHF (%)				Bleeding time according to Duke (minutes)				Bleeding time according to Ivy (minutes)				Platelet adhesiveness ac-coring to Salzman (%)			
	Before treat-ment	During treat ment	Pause	After treat ment	Before treat ment	During treat ment	Pause	After treat ment	Before treat-ment	During treat-ment	Pause	After treat ment	Before treat ment	During treat ment	Pause	After treat ment
9 III 1 ES	2.5	3.7	1.5		>30	>30	>30		>30	>30	>30		14	0	28	
	2.5	2.1			>30	>30	>30			>30	>30	>30		6	3	27
22 II 1 ID	32	24	11		>30	>30	>30		>30	>30	>30	>30	0	17	22	
	26	20	9		>30	>30	>30		>30	>30	>30		18	12		
38 IV 4 KS	25	25	18	21.3	8 7	9 16		6 6	23	>30	>30	>30	19	30	9	1
	29		7.3		9 13	15 1	>30		>30	>30			10	14	2	
42 III 26 EN	43	35	37	32	9 9	3 4	11 13	6>30	>30	>30	>30	>30	16	6	24	18
	30		10		2 5	3 9			>30	>30				0	31	

Graham (1959) suggested the possibility of different changes responsible for the tendency to bleeding in von Willebrand's disease to be inherited separately e.g. low AHF-content from one of the parents and prolonged bleeding time from the other.

In our material we were able to show bleeding symptoms in relatives of probands in 59 of 84 families (72 %) (Table 7). Certain signs of the occurrence of the disease in relatives have been seen in a further 15 families.

The investigation has corroborated the general opinion that the disease is inherited as an autosomal dominant.

The estimated penetrance in the investigation of parents was 73–90 %.

The expressivity varied widely often also within a given family. But with the analysis of variance we have shown that, as for the AHF-content, the expressivity is much more uniform within sibships than between unrelated patients ($p < 0.001$) Table 9). Affected children also resemble their affected parents in respect of AHF more than unrelated patients. The statistical significance of the X^2-test was $p < 0.05$.

The number of females among our patients with a firm diagnosis of von Willebrand's disease was larger than the number of males (Table 10). This may be because the disease is often manifested by uterine bleeding. It is of interest, however to note that among the cases judged as severe mainly from laboratory tests, there were 23 females and only 9 males. This might suggest a stronger expressivity among females than among males. But the figures are not large enough to warrant any conclusions.

Because of Graham's hypothesis, the chapter on heredity includes an analysis of the correlation between values for AHF and bleeding time for both the affected and the unaffected subjects studied (Table 11). We found a close correlation between reduced AHF-content and prolonged bleeding time. This argues against Graham's hypothesis.

We feel that the bleeding time and AHF-level are dependent on a common factor the von Willebrand-factor. The formation of this factor may in turn be influenced by one or more genes. Certain phenomena or circumstances such as physical and mental stress may then exert a temporary modifying effect on the amount and activity of the factor (page 108–109).

SYMPTOMATOLOGY

The symptomatology of von Willebrand's disease has been described in detail by von Willebrand himself (von Willebrand 1926 and 1931). But it appears that no serious attempts have been made to calculate the frequency of various symptoms in a larger series of patients with a firm diagnosis. We compared our frequency figures (Table 13) with Buchanan and Leavell's (1956) large compilation of published cases of "pseudohaemophilia" in which most of the patients probably had von Willebrand's disease. The comparison showed a fairly good agreement regarding the occurrence of bleeding from various organs.

The commonest types of bleeding were nose-bleeding, uterine bleeding, ecchymoses and haematoma,and bleeding after tooth extraction.

The haemorrhages that caused the greatest loss of blood are given in a special table (Table 14). Such heavy losses were most commonly found in patients with severe von Willebrand's disease and occurred particularly as postoperative bleeding, meno-metrorrhagia, gastro-intestinal haemorrhage and nose-bleeding.

As for nose-bleeding, we noticed that such bleeding often occurred at, or soon after other bleeding manifestations. Like Achenbach (1960), we often found that patients had considerable nose bleeding after surgical operations, even after operations on remote organs, such as the ovaries or the uterus. Such bleeding may have been due to consumption of AHF at and after surgery.

Traumatic bleeding of the lips and oral cavity proved to be a typical symptom of von Willebrand's disease in young children, especially in those with the severe form of the disease.

Traumatic bleeding does not otherwise generally cause a heavy loss of blood in patients with von Willebrand's disease. This may be because cessation of bleeding following severe trauma is more dependent on the coagulation mechanism, which is rarely seriously disturbed in von Willebrand's disease (see page 5). In addition, severe trauma results in the release of tissue thromboplastin. A low AHF-content will therefore be of less importance for the bleeding tendency.

A special group of traumatic haemorrhages are intracranial haemorrhages, and such bleeding proved fatal in two of our patients with the severe form of von Willebrand's disease (Table 16). The patients had a very low AHF level. In this connection the disease may be compared with haemophilia where intracranial haemorrhages have proved to be the commonest cause of death in recent years (Ramgren 1962, Blattner 1967).

Ecchymoses and haematoma were often the initial symptoms of the bleeding tendency. Petechiae were uncommon.

Menorrhagia was, as a rule, most severe among young girls the first few years after menarche (Table 18). It probably often occurred as anovulatory bleedings, intensified by the bleeding disease (see van Creveld and Schelleken 1969). One patient died and three were subjected to hysterectomy or roentgen castration before the age of 16 years. Some patients had anaemising menstruation throughout the age of reproduction.

Deliveries of women in the present material with the severe form of the disease occurred only under cover of Fraction I-O and fresh plasma. In the mild cases of von Willebrand's disease profuse post partum bleeding, requiring blood transfusions occurred in 8.6 of the females above 15 years. The corresponding figure in a normal population was 4.8 . Among females with mild von Willebrand's disease a heavy loss of blood occurred generally in association with obstetric complications. One of the reasons why heavy bleeding at delivery was relatively uncommon was certainly that AHF and the bleeding time had approached normal values towards the end of pregnancy. When bleedings occurred they often did so about one week or more after parturition (Fig. 1). This was probably because after delivery the bleeding times and AHF-values relatively soon return to their original levels.

According to various authors, particularly Horowitz and O'Leary (1965), abortion is relatively common in women with von Willebrand's disease. We could not confirm this postulation in our series in which abortion occurred in 9 out of 86 women who had been pregnant.

Ovarian bleeding, which is not often reported in the literature, occurred in 9 of our female patients, including 8 with severe von Willebrand's disease. In addition, some women were operated upon because of ovarian cysts which might have formed as a result of follicular bleedings.

In contrast with what was seen in several other forms of bleeding, gastrointestinal haemorrhage was most common in adult age. The bleedings were often serious and in 6 of our cases of certain or probable von Willebrand's disease they were fatal. One patient has for several years been disabled by recurrent gastric haemorrhage. Only in few cases had roentgen examination revealed ulcer or some other source of bleeding (Table 17).

Haematuria was uncommon and rarely serious. In three cases it was the symptom that brought the patient to examination and led to the diagnosis of von Willebrand's disease.

Joint bleedings in von Willebrand's disease are uncommon but were nevertheless seen in about half of our patients with severe von Willebrand's disease. A search of the literature and personal observations showed that when joint bleedings occurred, it was nearly always in patients with very low AHF values. In patients with AHF less than 10 (most often 1.5 5.0) in our series movement was sometimes permanently impaired in some of the joints but the patients were not disabled. Roentgen examination then showed bone and joint changes of the type seen in haemophilia.

Tooth extraction often causes profuse bleeding in von Willebrand's disease and in at least two of our patients such extraction was followed by a considerable blood loss. Bleeding after tooth extraction was sometimes obstinate and recurred in several cases about one week after the operation.

According to the literature, postoperative haemorrhage has otherwise occurred particularly after oto-rhino-laryngological and stomatological operations (Imerslund 1949 and others, page 100). Severe bleeding has been reported after hysterectomy (Hill & Taylor 1968 and others, page 101) while other abdominal operations are said to carry only a relatively slight risk of bleeding (Eriksson 1962 and others, page 101).

In the Swedish series only a few operations have been performed without specific prophylactic treatment in patients with the severe type of von Willebrand' disease (Table 22). Major operations in those cases have been followed by severe bleeding, and in one case the loss of blood after operation on a bleeding ovarian cyst was fatal. Even minor operations, such as uterine curettage, have been followed by serious bleeding complications in patients with the severe form of the disease.

Also almost half of the operations on patients with the mild type of von Willebrand's disease were, however accompanied or followed by remarkable bleeding (Table 23). Such postoperative bleeding was fatal in two cases of gastric resection. It was probably a main contributory cause of death in one case after thoracocentesis and in one after subtotal thyroidectomy. Life-threatening bleedings occurred after tonsillectomy and hysterectomy. Bleedings after division of the root of the trigeminal nerve because of neuralgia caused permanent neurological symptoms.

Bleeding after various operations have, as bleedings

after delivery and tooth extraction, often been obstinate with late exacerbations (Fig. 3 page 104).

Postoperative bleedings thus appear to constitute a severe problem in von Willebrand's disease. All operations on patients with the disease in the severe form and all major operations on patients with the disease in the mild form should therefore be given adequate prophylaxis. It is then also important that the operator is well aware of the patient's haemorrhagic disease so that he may pay special attention to haemostasis during the operation

Bleeding in von Willebrand's disease is most common during childhood and adolescence (page 105), and decreases notably with increasing age. Exceptions are gastric bleeding and postoperative bleeding.

DIAGNOSIS

In the present investigation the diagnosis was based on a bleeding tendency associated with low AHF and prolonged bleeding time, at least according to Ivy In the family studies the bleeding disease could, as a rule, be demonstrated also in some of the close relatives of the probands. In several cases platelet adhesiveness according to Salzman was found to be reduced. On administration of Fraction I-O or fresh plasma it was ound that the AHF rose successively and that the blee time usually became shorter The criteria for the diagnosis were more rigorous for the probands than for their relatives (see page 13).

The evaluation of the patient's history and the examination methods have several sources of error In addition, the results of laboratory studies vary owing to such factors as physical exertion, mental stress, infection and pregnancy (see pages 108–110). We were also able to demonstrate a slow rise of the AHF with age (see page 109).

These sources of error create difficulties in the diagnosis, especially of the mildest cases with borderline values. In such cases some of the examination findings are not infrequently normal, while others argue for the presence of the disease in the mild form. In the investigations of relatives it was often difficult despite repeated examinations to decide whether a person had the disease or not. We then used the term "intermediate results Genetic evaluation with regard to the probable frequency of the disease in parents and children of the probands suggested that in these cases we were dealing with persons predisposed to the disease but in whom, owing to weak expressivity the disease had not become manifest.

The relation between the bleeding tendency and the results of laboratory studies were judged with the aid of correlation tables (see page 111). The bleeding tendencies of the different patients were graded and related to mean values for AHF bleeding time according to Duke and according to Ivy and platelet adhesiveness according to Salzman. The tables showed a closer correlation between the bleeding history and values for AHF and bleeding time than between history and values for platelet adhesiveness. But the bleeding time according to Duke was usually normal in patients with a mild predisposition to bleeding and often also in patients with moderate bleeding symptoms. On the other hand, in many cases the bleeding time according to Ivy rose to more than 30 minutes, even when the bleeding tendency was very mild.

The values obtained with the different examination methods were also related to one another (Tables 35 –39). Statistical calculation with rank correlation (Table 40) showed a clear correlation between deviations from the normal concerning AHF and bleeding time. The correlation was less clear when platelet adhesiveness according to Salzman was correlated with other laboratory values.

The correlation found between AHF and bleeding time is of particular interest in the discussion of the inheritance in von Willebrand's disease (see page 84).

In the differential diagnosis of von Willebrand's disease the condition must be distinguished from mild haemophilia A, thrombasthenia and primary platelet dysfunction. In three families we encountered diagnostic difficulties in the distinction of von Willebrand's disease from these diseases. We established the diagnosis by administration of Fraction I–0 and following the AHF values and bleeding time for the next few days

PROGNOSIS

Patients with severe von Willebrand's disease may have severe bleeding symptoms during childhood and adolescence. The symptoms, however generally improve later and even in severe cases the prognosis is, broadly speaking, good, especially with the therapeutic possibilities now available.

Deaths from bleeding have been compiled partly from the literature and partly from the present material

(Table 43). The distribution of these cases among different bleeding symptoms is fairly similar in the two complications. Gastric bleeding has been the commonest cause of death followed by intracranial bleeding and postoperative bleeding. Haemoptysis has formerly sometimes been the cause of death from haemorrhage, probably most often in cases of tuberculosis.

It is thus important that gastro-intestinal bleeding in patients with von Willebrand's disease be carefully treated. Head injuries and major operations require specific prophylaxis of bleeding, especially in severe von Willebrand's disease.

Considerably reduced working capacity has occurred mostly as a result of frequently recurrent gastric bleeding and menorrhagia. Joint bleeding has occasionally resulted in permanent impairment of range of movement of joints, but has not caused disability of the type seen in severe haemophilia.

Menorrhagia and heavy bleeding at delivery has sometimes made it necessary to perform hysterectomy or roentgen castration. Present therapeutic methods with hormone preparations can probably now make such operations unnecessary.

The risks of the child of a patient with von Willebrand's disease developing clinically manifest bleeding symptoms is, as judged from genetic studies in our material, about 40 %. The probability of severe bleeding symptoms is much smaller: barely 5 %, and it appears to be less important whether the affected parents have the disease in the mild or severe form. If parent has severely ill child, the risks of later children also having severe bleeding symptoms is considerable. Thus, in three of our families two siblings have severe von Willebrand's disease but in only one family has one patient the severe form of the disease and a sibling the mild form.

THERAPY AND PROPHYLAXIS

The discovery of AHF-deficiency and deficiency of an inhibitor of bleeding in the plasma (the von Willebrand-factor) has made it possible since the middle of the 1950s to offer specific prophylaxis and therapy for bleedings in von Willebrand's disease.

At operations and tooth extractions, Fraction I-O and fresh plasma have been given prophylactically to Swedish patients with von Willebrand's disease (Tables 44, 45 and 46). With such prophylaxis it has been possible to perform major operations also upon patients with the severe form of the disease. Only in a few cases have serious bleeding complications occurred. The occurrence of an anticoagulant was suspected in one case. It has proved necessary to continue treatment for a sufficiently long time after the operation since postoperative bleeding of patients with von Willebrand's disease often occurs relatively late, i.e. after about a week or more. Treatment with fresh plasma alone has, as a rule, not been able to prevent postoperative bleeding after operations on patients with severe von Willebrand's disease and sometimes not after major operations on patients with the mild form of the disease.

In two cases delivery of patients with the severe form of the disease and with low AHF required extensive therapy to cope with the prolonged bleeding tendency from the vagina in the puerperium (Table 47).

Spontaneous bleeding, refractory to local measures has proved to respond favourably to Fraction I-O and fresh plasma (Table 48). The bleeding usually promptly ceased but sometimes required intense prolonged therapy, especially gastric bleeding.

The effect of Fraction I-O and fresh plasma on AHF, bleeding time and platelet adhesiveness, was studied. It proved possible to maintain AHF at desired level, except in two cases with signs of circulating anticoagulants. The bleeding time according to Duke could, as a rule, be promptly normalised, but only for short time. With the doses used and given at intervals longer than 12 hours it was sometimes not possible to maintain a normal bleeding time in severely ill patients. Preparations of Fraction I-O manufactured in large batches from fresh frozen plasma have sometimes had a less satisfactory effect on the bleeding time. When the bleeding time was severely prolonged, bleeding often occurred despite high AHF-values. The bleeding time according to Ivy responded but little to the specific therapy. Platelet adhesiveness according to Salzman was not affected by the treatment.

As for side-effects, signs of anticoagulants have been observed in one patient, who had received treatment with Fraction I-O and fresh plasma. One patient developed moderately severe hepatitis after treatment with Fraction I-O. Otherwise no serious complications occurred.

The result of treatment with ε ACA and AMCA is difficult to judge because, as a rule, the patients ha received also some other treatment.

Corticosteroids have been tried in one case but without success.

In menorrhagia modern oral contraceptives have proved to have a favourable effect. In 4 cases where the laboratory values were followed it was, however not possible to demonstrate any obvious effect on the AHF bleeding time or platelet adhesiveness (Table 50). The effect on menorrhagia therefore seems to be ascribable mainly to a local effect on the endometrium. The patients, however felt that during treatment with p-pills" they had reduced bleeding tendency also from other organs.

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ADDENDUM

In 1971–1972 important observations made at the Coagulation Laboratory Malmö have influenced our conception of von Willebrand's disease. These observations are briefly summarised in the following Addendum by Lars Holmberg.

GENETIC VARIATIONS OF VON WILLEBRAND'S DISEASE

by

Lars Holmberg

von Willebrand's disease is characterised by a low AHF-activity in the plasma and a prolonged bleeding time (Nilsson et al. 1957). These criteria together with reduced platelet adhesiveness, as measured according to Salzman (1963), have hitherto constituted the diagnostic criteria for von Willebrand's disease. Typical of the disease is also the response to infusion of factor VIII concentrate (Fraction I-O, cryoprecipitate). Infusion of such concentrates in patients with von Willebrand's disease normalises the bleeding time and often produces a retarded increase of the AHF activity in the plasma. This effect has been ascribed to the von Willebrand factor, i.e. a plasma factor lacking in von Willebrand's disease but occurring in normal plasma and in plasma in haemophilia A (Nilsson et al. 1959, Cornu et al. 1961).

Recent years have, however, witnessed the development of further possibilities of diagnosing von Willebrand's disease as well as an increase in our knowledge of the molecular nature of factor VIII in the plasma and the relation of this factor to the von Willebrand factor. The AHF activity is linked to a very high molecular weight plasma protein complex. This complex can be isolated, and the method generally used is gel chromatography in agarose (Hershgold et al. 1967, Johnson et al. 1967, Paulssen et al. 1969, Ratnoff et al. 1969, van Mourik & Mochtar 1970). Investigations using an immunologic technique have shown that patients with haemophilia A possess this protein complex, but in a biologically inactive form. Investigations by Stites et al. (1971) and Zimmerman et al. (1971) in a few patients with von Willebrand's disease suggested that these patients have little or no AHF related antigenic material in the plasma.

Some of the Swedish patients with von Willebrand's disease presented in this thesis have now been examined immunologically for AHF related antigen. The AHF activity was isolated from human Fraction I-O by agarose gel chromatography (chromatography in agarose gel) in a buffer system containing Rheomacrodex® according to van Mourik and Mochtar (1970). UV absorbing material appeared with the void volume and contained most of the AHF activity recovered. The fraction appeared homogenous. Thus fibrinogen, γ-globulin and α_2-macroglobulin could not be demonstrated immunologically. Rabbits were immunised with this fraction and a monospecific antigen was prepared. This produced only one precipitation line with Fraction I-O and with plasma. Antiserum has anti-AHF activity in an *in vitro* test system with plasma (Holmberg and Nilsson 1972).

The amount of AHF related antigenic material was determined by Laurell's method of electrophoresis in agarose gel containing antibodies. The electrophoresis was run in 0.075 M barbital buffer, pH 8.6, with 0.01 M EDTA. The analysis was carried out on plasma. If the plasma contains only little AHF related antigen the precipitation line tends to be less well defined, especially if the content is less than 10 to 15 % (of normal). The analysis was therefore performed also on cryoprecipitate of plasma from patients, and then it was possible to measure the lower concentrations. The agreement between the values found in plasma and in cryoprecipitate was good.

Twenty-three families from the Swedish series of von Willebrand's disease have so far been examined with the immunological method (Holmberg and Nilsson 197?). It was found that 51 patients belonging to 15 families had a low content of AHF related antigenic material. All affected members of these families had low values, while unaffected members had normal values. However, 19 patients belonging to 8 families had normal values of AHF related protein. All affected members of these 8 families showed the same pattern. Judging from these investigations, there appears to be a genetic variation in von Willebrand's disease. In type 1 of the disease the content of AHF related protein is always low. In type 2, on the other hand, it is normal, as in haemophilia. The families with type 1 and type 2, respectively, are given in Tables 1 and 2. The most severely affected patients with type 1 of the disease have also the lowest content of the AHF related protein. Patients with mild symptoms of the disease have only moderately reduced values.

In families belonging to type 1 the mode of inheritance is well compatible with autosomal dominant heredity. Examples of transmission of the condition from the father to the son are families 5, 6, 14, 17, 42, 58.

In the 8 families with von Willebrand's disease of type 2, i.e. with a normal content of AHF related protein, none of the affected males had had affected sons, and of the members studied, none of the affected men studied had healthy daughters. Examples are families 55 and 100. The mode of inheritance in these families are obviously X-chromosomal. As a rule, the male members had symptoms more often than the females, in whom the disease was discovered in family studies of members who had often had no symptoms. They were thus sometimes only carriers of the disease.

It would thus appear as if von Willebrand's disease, which has hitherto been regarded as a single clinical entity with a unique molecular pathology is in reality separate diseases. Type 1 corresponds to the classical type of von Willebrand's disease with prolonged Duke bleeding time in severe cases and, as a rule, with low platelet adhesiveness according to Salzman. Severe cases with prolonged Duke bleeding time also occur in type 2 but, as a rule, the Duke bleeding time is normal and only the Ivy bleeding time prolonged. Further adhesiveness according to Salzman is often normal. It appears that von Willebrand's disease type 2 is a separate disease with a clinical picture closely resembling that of the classical type of von Willebrand's disease, but with certain features resembling those of mild haemophilia A, especially regarding its mode of inheritance. Occasional families with similar characteristics have been described previously (Egeberg 1965).

Further research of the molecular structure of factor VIII may help to reveal the relationship between the two diseases.

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Table I
Families with von Willebrand's disease Type I

	AHF					
	Activ	*Imm*	*Ivy* (min)	*Duke* (min)	Salzman *	*Symptoms*
Fam. 1						
EB	20	0		>30	10	Severe
BT	8	0		>30	7	Severe
Fam. 5						
PP	23	29	30	9	9	Mild
WP	28	38	21	16	6	Mild
Fam. 6						
AF	60	36	19	5	3	Mild
RF	6	7	>30	>30	10	Severe
Fam. 10						
MA	10	<1	>30	>30	0	Severe
Fam. 11						
GB	24	6	>30	>30	3	Severe
Fam. 12						
KPA	5	0	>30	>30	2	Severe
Fam. 14						
BJ	20	11	>30		0	Mild
GJ	19	8	>30	8	0	Mild
LJ	38	19	>30	6	0	Mild
RJ	39	8	>25	3	10	Mild
Fam. 17						
LL	41	20	>30	2	61	Mild
Fam. 23						
KW	26	5	>30	>30	13	Severe
Fam. 42						
HN	43	18	>30	8	0	Mild
AS	47	33	>30	2	0	Mild
IA	42	27	25	4	5	Mild
SP	79	27	>30	24	2	Mild
IN	48	25	30	2	35	Mild
AF	36	16	>30	5	7	Mild
KE	29	10	>30			Mild
NA	54	23			10	Mild
BA	38	30	28	4	1	Mild
KS	43	12		23	7	Mild
JIA	44	27	>30	2	6	Mild
LA	58	50	17	1	0	Mild
P	55	53	>30	5	39	Mild
JEF	48	17	15	2	31	Mild
JN	40	17			0	Mild
ME		11				Mild
HE	30	12		4		Mild
AA	37	27	>30	3	19	Mild
GA		28			4	Mild
PS	1	19	>25	8 – 15	34	Mild
BIS	53	23	30	4	0	Mild

(continued)

	AHF* Actv	Imm.	Ivy (min)	Duke (min)	Salzman	Symptoms
Fam. 58						
KF	45	23	>30	8	11	Mild
IF	45	13	>30	7		Mild
AF	40	37	>30	5–30	0	Mild-Severe
Fam. 60						
LJ	35	15	>30	8		Mild
MB	48	17	<3	2	18	Mild
MJ	63	25	30	6		Mild
LJ	30	7	>30	>30		Severe
AB	62	33	15	5	3	Mild
JB	33	21	21		14	Mild

Table 2
Families with von Willebrand's disease Type II

Fam. 28							
AS	m	16	225	>30	>30		Severe
JBK	f	38	110	19–9	4	15	Mild
LH	m	47	112	>30	5	24	Mild
RH	m	27	75	24	3	47	Mild
IN	f	26	122	15–18	4	19	Mild
AK	f	25	87	15	4	6	Mild
Fam. 55							
MBP	f	59	120	12	3	0	Mild
LF	f	52	122	12	3		Mild
GF	m	32	144	>30	3		Mild
RF	m	33	116	15	4	89	Mild
Fam. 100							
MS	f	35	72	19	3	30	Mild
AS	m	20	88	30		49	Severe
Fam. 107							
MB	f	45	124	>30	7	11	Mild
CB	f	77	91	>30	11		Mild

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THE FINNISH SKOLT LAPP CHILDREN

A CHILD PSYCHIATRIC STUDY

BY HARRIET FORSIUS

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM

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Head Professor Kauko Kouvalainen, M. D

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a child psychiatric study

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Introduction

The child's growth environment that many sided concept which includes geographical, climatical, cultural, sociological, psychological and emotional factors, has a great effect on the individual development of the child's personality and on his psychic balance Inherited aptitudes naturally also play a part in the child's personality The question as to how far these different factors, genetic aptitudes and environmental conditions respectively affect the development of personality can probably not be definitely answered as long as the child is studied in its natural growth environment, where his parents behaviour possibilities of safeguarding the child's existence, and attitudes towards his upbringing are affected by their personal characteristics. These in turn, create the atmosphere of the child's physical, mental and emotional development.

The atmosphere of development is different for each individual child, depending on the particular personal relationship between the child and its immediate surroundings. It contributes towards the creation of a personality that is psychically harmonious or one that shows signs of psychic disturbance In every group of people, there are always individuals who in some way differ from the standards current within the group Within that same population group, however uniform standards, concepts morals, ways of thinking and practices prevail, in other words, everything we usually sum up with the word »culture» Whether and in what way a people's special culture moulds the individuals living within it, has long been an important subject of research. However it is only in the last few decades that the psychiatrist and the anthropologist, each approaching the problem from his own particular angle, have drawn nearer together in the attempt to produce a synthesis.

It is difficult to distinguish between all the above factors that affect the child's development. However a small homogeneous population group with distinctive cultural characteristics could be expected to provide better opportunities for differentiating between its various structural components.

The Skolt Lapps live in North Finland and make up a genetically homogeneous group which, to date, has lived in relative isolation, and has its own distinctive culture. The number of population, about 600 individuals today is sufficient to provide investigation material and not too large for an overall view

Despite the fact that the Skolt Lapps have their own culture which in certain respects is different from that of the Finnish population in general, they are neither geographically nor linguistically too far from us. We have every opportunity to obtain a detailed knowledge of the Skolt Lapps customs and way of thinking their concepts and ideology

The Skolt Lapps are now closely exposed to the Finnish social structure. It is an open question whether they will be able to retain their identity or whether in the near future, they will be assimilated into the Finnish culture. Such an assimilation could at least be delayed if we were able to motivate especially the young generation to accept and take a pride in their own identity and to preserve what is valuable in their own culture

Purpose of the study

The Skolt Lapps in Finland are a population group that since the beginning of this century has been studied from many angles by scientists in various fields medicine physiology anthropology sociology and ethnography We are aware of many background factors within this population group which are of importance for the child's development It can therefore be considered appropriate to study the Skolt Lapps also from the point of view of child psychiatry, and to try to find out whether the special conditions under which Skolt Lapp children live have left any mark on their psychic development.

In order to find out whether the state of psychic health among the Skolt Lapp children is peculiar to them, a group of Finnish children was examined by the same methods, since few epidemiologic studies on a child psychiatric material have ever been carried out in Finland

The purpose of the present study is

(1) to obtain an overall idea of the psychic and somatic state of health among the children of Skolt Lapps in Finland

(2) to find out whether any characteristics of child psychiatric importance occur among the Skolt Lapp children, and whether the possible distinctive characteristics depend on the particular cultural factors of Skolt society such as the parents special attitudes towards bringing up children,

(3) to find out whether it is possible to distinguish any genetic aptitudes which might be of importance in the development of Skolt children

Review of the literature

A. ETHNOGRAPHIC BACKGROUND OF THE SKOLT LAPPS

1 History

The origin of the Lapps

Research today holds that the Lapps form an ethnic group that invaded Scandinavia from the eastern parts of Central Europe, probably already during the final phase of the glacial period, when they followed the retreating ice blanket and wild reindeer herds towards the northwest. Archaeological prehistoric finds, e.g. of skis estimated to be about 4000 years old, suggest that the Skolts at that time already populated the coasts of the Arctic Ocean (Nickul 1970)

A number of archaeologists believe that the ancestors of the Lapps had originated from a mixed group which included people belonging to the oldest known Scandinavian Stone Age culture, the so-called Komsa culture (Wiklund, cited by Nickul 1970)

Linguistically the position of Lappish is uncertain. The language is, presumably in part a relic which has, however been strongly influenced by the earlier Baltic Sea Finnish.

Anthropometrically Skolt Lapps are characterized by short stature and certain special features of skull structure and facial form which suggest kinship with East European or Mongolian peoples. Some of these special features, especially the height growth, depend, however not only on genetic factors but largely also on external circumstances, food supply etc. (Lewin and Hedegård 1971)

Serologic studies show gene frequencies that suggest both an Eastern and Western influence. Variations within the different Lapp groups can, however be considerable. The frequency of blood group A is high among the Lapps, the gene A_2 having a frequency 2—4 times that among the other Scandinavians, in whom the frequency is about 5—10 In no other population has an equally high frequency of the gene A_2 been recorded. Also, the Lapps have an extremely high frequency of the erythrocyte-acid phosphatase gene P^a which is completely non-existent among the East Asiatic peoples studied to date These characteristics suggest a Western influence in the Lapps' origin. An Eastern influence is suggested by the fact that the frequency of the d-gene in the Rhesus blood group system in all Lapp populations studied to date is markedly lower than among other Europeans. Furthermore, it has been found that the frequency of blood group B increases eastward, and so does that of gene M in the MNS system. On this point there are variations within the Lapp groups The Skolt Lapps show both a high frequency of gene B and a relatively high frequency of gene M, whereas the frequency is on the low side among the other Lapp groups (Eriksson 1967 1968, 1971 Eriksson et al. 1970)

Skolt Lapps

The Lapp population is estimated to total something like 35 000 individuals of whom about 20,000 live in Norway 10,000 in Sweden, 3,000 in Finland, and 1,500—2,000 in the Soviet Union (Nickul 1970 Ruong 1969)

The Skolt Lapps constitute a minority within the Lapp population. They have their own language which essentially differs from the other Lapp dialects.

The distinctive character of the Skolt Lapps, compared with the other Nordic Lapps, has its origin in the Skolts' different cultural-historical background and the fact that for long periods they have lived in greater isolation than the other Lapps. It is known that Skolt Lapps, at least since the late Middle Ages, have inhabited areas of the Kola Peninsula the Neiden district at the Varangerfjord in North Norway the Pasvig (Paatsjoki in Finnish) — Petsamo district on the coast, and the Suenjel (Suonikylä in Finnish) district in the interior western area of the Kola Peninsula (Fig 1) The border with Norway and Finland prevented intercommunication with Scandinavia and the Russians were more interested in the Kola coastline than in the interior of the peninsula which, at any rate in the summer was inaccessible. After the Peace of Tartu (Dorpat) Petsamo and a large part of the Suenjel district were incorporated with Finland in 1921 The Finnish Settlement Act of 1925 concerning the Petsamo district was, however not applied in Suenjel. As a result, the Skolt social structure could be largely retained in its original forms until the outbreak of the Second World War in 1939 (Nickul 1970)

Life within the 'sijd'

The families formed sijds Lapp villages, usually along a route of communication. The land areas and fishing waters were considered to belong to the 'sijd' and the families had only the use and enjoyment of these areas. However the same areas were used for centuries by the same families, although repartitioning was carried out when necessary Despite the reindeer herds, the main means of subsistence was provided by fishing and hunting The catch was evenly distributed between all inhabitants of the 'sijd' the old and sick who could not take part in the work also receiving their share. In this way no major differences

Purpose of the study

The Skolt Lapps in Finland are a population group that since the beginning of this century has been studied from many angles by scientists in various fields: medicine, physiology, anthropology, sociology and ethnography. We are aware of many background factors within this population group which are of importance for the child's development. It can therefore be considered appropriate to study the Skolt Lapps also from the point of view of child psychiatry, and to try to find out whether the special conditions under which Skolt Lapp children live have left any mark on their psychic development.

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(3) to find out whether it is possible to distinguish any genetic aptitudes which might be of importance in the development of Skolt children

samo district in the 1920s. By the time the Second World War broke out in 1939 their economic standing had somewha improved.

Changes during and after the Second World War

At the outbreak of war in 1939 the Petsamo district came within the sphere of military operations. The Skolts were evacuated to Tervola, in North Finland, where they stayed for bout 4 months. From 1940 to 1941 there was year of peace, and during this time they returned home. When war again broke out between Finland and the Soviet Union the Skolts stayed in their homes until Petsamo once more became too unsafe in the spring of 1944 They were then evacuated to North Ostrobothnia. After the armistice in 1944 when the Petsamo district was ceded to USSR, the Skolts preferred to remain Finnish citizens. They lived in temporary dwellings for two years until the state assigned them land areas east of Lake Inari in Lapland, in place called Nellim, 30 km from the village of Ivalo. However the Suenjel Skolts in particular wished to resume their former principal occupation, reindeer breeding. They approached the authorities gain nd were assigned land area north of Lake Inari, the area of Sevettijärvi which had earlier been the winter illage of the Neiden Skolts. Forty families, total of 267 persons, settled here while 20 families, comprising 140 persons, preferred to remain in Nellim.

The state built houses of 34 sq.m. for every family They consisted of one room and kitchen, and there was store-shed and 'sauna as well. A school with boarding-house adjoining, and a health centre, were also constructed. Similar houses were built for the Nellim Skolts.

2. *Demography*

The present Skolt population is presumed to be descended from few families. The earliest record concerning the size of the Skolt population dates back to 1574 and refers to the Suenjel 'sijd' where the population totalled 21 persons distributed between four kota-huts. I 1610, total of 56 Skolts were registered the whole population of Finnish Lapland that time amounted to some 1100 persons (Tanner 1929) The Skolt population has increased gradually and in 1963 there were 515 persons (259 men and 256 women) in Finnish territory The total population of genuine Skolts shows substantially larger increase than other groups of Lapps in Finland. This is explained by the higher *birth rate* among the Skolts, and by the fact that their assimilation with other population groups has been considerably less than that of the Lapps in general. The increase, however pplies only to the Sevettijärvi Skolts. The number of Nellim Skolts has come to standstill owing to their greater assimilation. Mortality rates mong the Skolt Lapps rose sharply during the war years of 1940—44.

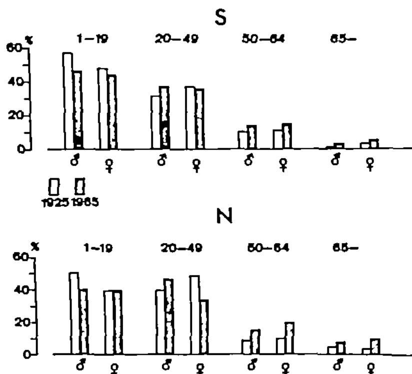


Fig 2. Age distribution in Sevettijärvi (S) and Nellim (N) Skolt Lapp population groups in 1925 and 1965 (Lewi et al. 1971)

Since 1950 the rate has again decreased perceptibly tha ks t improved living conditions. Age distri bution among the Skolts is shown i Fig. 2 (Lewin et al. 1971 a)

Infant mortality among the Skolt Lapps has been high. I the war years of 1940—44 about 15 of the children died before the age of 1 year and in the post-war period right up t 1954 the infant mortality rat among the Skolts was around 8—10 %. Subsequently however infant mortality has successively decreased in 1955—59 it was ca. 6 and in 1960—64 ca. 4 %. Compared with the rest of Fenno-Scandia, where the infant mortality rate is about 1.5 %, this is still high, but it applies mainly to the Skolt population that has been living in isolation (Lewin et l. 1971 b)

Now that road connections ha been improved, it is probable that the Skolt population of Sevettijärvi will lso, i the long run, be assimilated into the surrounding population

3 *Religion, popular belief and fairy-tales*

As with the other Lapps, the age-old paga belief were deeply rooted mong the Skolts. Early in the 16th cent ry Mitrophan, who was the son of Russian priest and eventually became St. Triphon, lived among the Skolt Lapps i Petsamo t convert them t the Orthodox religion However it took twenty years before mall proportion of the inhabita ts wer ripe for his doctrines. During these yea he was many time close t losing his lif since the shamans in particula were very much gainst him (Hämäläinen 1938)

Together w th the Skolt Lapps and with helpers from Russia, St. Triphon built small church in Petsamo, completed 1533 and founded monastery housing the first monks from mong the Skolts. The monastery flouri hed in the 1550s but was destroyed during the w 1 1590 not t be re built il 300 years later The Skolts ha remained Greek-Orthodox but since the destruction of the monastery the Russian influence has not been particularl trong

The doctrines of Orthodo Christiani y never seem t has become ery deeply rooted mong the Skolts. Divine service was seldom held in the sparsely populated county nd the Suenjel Skolts especially had little contact w th the few priests. Even since the war services have only been elebrated few times yea in the Skolt settlements in Finland.

There many indic tions that the Skolts faith is ombination of Christianity nd their primitive belief (Hämäläinen 1938, Itkonen 1918, Storå 1971) Grea re was devoted t the dead for it wa believ ed tha hey till had power over the li ing nd would sometimes come back ei her to haunt them or possibly help them They could also be reincarnated in newborn baby named after deceased lative Children were of en given doubl names t confuse L evil piri

It is not long sinc reindeer sacrifices were offered the dead for bear f ur need nd all kinds of h sehold utensil were buried wi h hem. Later it w sid ered enough pu the spade w h which he gr ha been dug he of in, and also ax for no Skol Lapp would se foot in he forest w thou an S rå 1971

The Lapps seita worship is form of primitive animism or fetishism. Stones, logs and other lifeless objects, which for some reason specially ttract the attention of the primitive people re invested with life and imagined t house a pirit. Consequently they re thought to possess a mysterious, supernatural power and have been the objects of actual worship (Karsten 1952) 'Seitas could still be met with in Petsamo i the 1930s (Hämäläinen 1938)

In ddition to seitas the Skolts ho believed in other beings, such as the household fairy who lived beneath the fireplace, ta aj' the guardian of the hunt, and reindeer fairy who lived on the moors where the reindeer lichen grows and had the appearance of hairy man (Hämäläinen 1938)

Stories of malicious beings, .g stalem-stalli' were f equent (Itkonen 1918) As protection gainst these, there were shamans mong the Skolts who by incantations nd other magic were ble t ppease the supernatural powers. Until the 1920s the Skolts still had thei medicine men who acted both as doctors and as counsellors (Paulaharj 1921).

Animals, particularly the bear play important part i Skolt mythology Skolts never eat bear meat, probably because they belie that the bear can take th guise of man. T les are told of how a slaughtered bear was found to have a belt f lled wi h gold coins inside its skin, nd onc even a dead Skolt was found there.

Many of the Skolts other fairy-tales re international stories telling bout kings nd princesses. Some ha moral end ng where virtue is rewarded and si is punished. Other fairy-tales are intended to teach the children obedience, e.g the story of the wolverine which popped hildren in its bag if they stayed out too late, sledging (Pal ämalo 1953)

Although radio, newspapers nd books ha e largely suppla ted the old custom of telling nd listening to folk tales and stories, it may st ll happen, in the long wi er evenings when the family is assembled i the hut, that one of the elder folk will call to mind an old fairy-tale.

Many of the adult Skolts could, i all seriousness, tell stories bout ghost nd bout the places where dead people walked again. There was, for example, the young man who i 1968 w teering our motor boat on an expedition t the dista t Lake Kirakkajärvi. When da kness fell and the mist bega to rise he was scared to death that w should ru onto the *tone where few years earlier the W ter Spirit had* claimed life and Skolt had been drowned.

4 *The present-day situation*

A cording to the data of the 1960 census, the raising of reindeer is the most importa t sourc of income for the Lappish-speaking Skolts (Asp 1967) The reindeer stock was estimated t bout 4 000 head in the 1960s.

In the summer of 1970, after the present study had been carried out, new road passing through Sevettijärv to the north t the illage of Neiden on the Norwegian side was completed. Until then, inhabitants of Sevett järv living north of the mai illage had mostly done their shopping on the Norwegian side walking the 20 km there nd back. There is now daily bus connection with Ivalo, and the illage has its own post of ice and shops.

Nellim had always had good road connections with Ivalo, and contacts with the outer world, such as mail and radio, were better than in Sevettijärvi.

According to Asp (1967) the housing situation is one of the worst shortcomings among the Skolt Lapps. I the dwellings built by the state, the floor area per inhabitant was only just over 4 sq.m., less than in any other area in Finland. Only few of the more go-ahead Skolt families have found ways and means of renovating or enlarging their homes. On the basis of the 1960 census, Asp calculated that overcrowding occurred in 31.8 % of all households in the rural communes of the Province of Lapland, against 62.7 among the Skolt Lapps.

Only the school and health centre of Sevettijärvi have electric light. The dwellings have no modern conveniences.

B SOCIO-ANTHROPOLOGICAL ASPECTS

1) *Culture and personality*

Anthropologists and sociologists have contributed to the knowledge of the child s behavioural development by studying primitive people. Among these the child is often the main organ or instrument in the perpetuation of culture. On the other hand, the child s individuality is formed by the tribal beliefs and moral code (Miller 1928) The relationship between personality and culture is discussed by Arieti (1955) according to whom one opinion held by Fromm (1968) and Sullivan (1947) among others, is that man is largely a product of his environment, in other words, of the culture to which he belongs. Another opinion, based on Freudian theories sees the personality and culture more as a result of man s instinctive needs. The real seat of culture is considered to lie in the interaction between the individuals and the fact that each individual more or less consciously accepts whatever in the culture is of importance to him personally and through his participation actively contributes to maintaining the cultural values (Sapir 1938)

Various societies display especial personality norms (»national character» »model personality») Except in cultures subject to rapid changes, this model personality strives to be congruent with the culture. Persons who are steeped in their own culture experience a minimum of frustration and a maximum of reward (Linton 1956)

The varying frequencies of different personality types among different cultures (i.e., a high frequency of aggressive men among the warlike Comanches) are explained by Linton as an indication of a genuine correlation between child rearing and the type of personality characteristic of the society in question.

The complexity of society and of personality makes it difficult however to isolate a factor and demonstrate the effect of a single component on the individual s whole personality (Linton 1956 Opler 1956) E. Erikson (1950) points out that simplification to the extent of believing that the treatment given to an infant produces special traits of character in a group of adults, is not possible. This would mean in other words, that by pushing certain buttons in the upbringing of children, certain national characteristics could be created He prefers to speak of goals and values which are upheld because they have become essential parts of the individual s concept of his identity How ever values are not retained unless they prove to be effective in economic, psychological and mental respects.

These values are perpetuated from generation to generation in child rearing which in turn is built on a continuous synthesis of culture and social life. This striving towards a synthesis in culture draws closer together such factors as climate and anatomy economy and psychology, society and child rearing and makes them reinforce each other

The necessity of seeing the growing child as functioning within his entire social group is emphasized by Mead (1966) in her review concerning the study of primitive children. The research worker must be familiar with the child s speech, his way of thinking the content of his thoughts, with the child s ability to feel and the way in which emotions are expressed and with the whole interaction between the external and internal factors, before it is possible to operate with concepts such as the »Zuni child» and the »Arapesh child»

However it is difficult to ascertain possible relationships between socio-cultural and psychiatric variables, even if

exact incidence gradings are used, owing to the dissimilarities in the culture and the difficulty of drawing the line between normal and abnormal according to the standards of the unfamiliar culture (Chance 1966 Leighton 1953) There is no concept concerning culture or personality that is universal and generally applicable (Wallace 1961)

The literature on child rearing among so-called primitive peoples is extremely extensive. Most ethnographic writings contain descriptions of child care and the bringing up of children (review of the literature up to 1936 Jansson) but only since the Second World War have the efforts towards systemization been intensified by research.

Research teams (e.g Whiting and Child 1958) have tried to relate the child's personality development to his care and upbringing starting from the cultural background The authors are mainly interested in oral anal and sexual behaviour and in dependence and aggression, with the motivation that all these five dimensions occur and are exposed to attempts at socialization in all societies. These analyses however were made on ethnographic data from anthropological literature

B. Whiting (1963) reports on field studies among six cultures and gives a schedule (Fig 3) for visualization of the relationship between the child's upbringing and his personality The child's personality is judged according to his behaviour *that of the adult according to his* behaviour popular beliefs and values. Environmental factors, social economic, climatic etc. would consequently determine the forms of child rearing These forms are then rationalized and gain support from conceptions and cultural values In other words it is not values and popular beliefs that create the basis for the pattern of child rearing The author p[illegible]nts out however that cause and effect i[illegible] a matter of opinion and mentions an[illegible]ther cont[illegible]t Whiting J and Whi[illegible]t[illegible] B [illegible] Rajput mothers in N[illegible]rt[illegible] India, believ[illegible]g that th[illegible] child's des[illegible]tiny i[illegible] written on it[illegible] [illegible]ehead and that both health, temperament and behaviour ar[illegible]

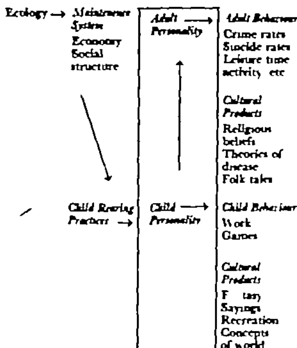


Fig 3
Relationship between environment, culture and personality (from Six Cultures ed. by B. Whiting)

predetermined are considerably less interested in questions concerning the children's upbringing than are the mothers of New England. The latter believe that the child is born with innate possibilities of development and that this can be affected by parents, teachers and friends. These mothers showed a considerably greater interest *in problems of upbringing* The same opinion of the role of the environment in upbringing is advanced by Minturn and Lambert (1964) who studied the mothers attitude in the same six cultures. The mother's attitude to her child depends on her own problems, and not on theories of child upbringing The authors, however studied a limited material of only 24 mothers within each culture

Numerous studies have been carried out concerning diverging backgrounds within a single culture or in various subcultures in the community, and their relationship to the child's development Most research workers have pointed out, however that the parents attitude to children and to

questions of upbringing can vary within the same culture and even for the same parents at different times, e.g. in relation to the child's order of parity (Minturn and Lambert 1964, Chess 1969). A review of the studies concerning family variables and a possible correlation to the children's development has been published by Hoffman and Lippitt (1960). Jones (1966) tries to estimate the importance of various factors in the personal environment on the development of the child's character and points out that all factors ultimately operate within the framework of the general culture, »over all culture». According to K. Lewin (1966), the ideology, values and attitudes of the growing individual depend largely on whether he or she belongs to a privileged or an under-privileged group.

2. *Child rearing among Arctic people*

In primitive cultures, learning is often acquired informally by imitation (Miller 1928, Päivänsalo 1953, Havighurst 1957, Pelto 1962 and others). Guterman (1965), reporting on Eskimoes, says that although knowledge was mostly gained by observing the parents or the parents' siblings, the whole village participated in the upbringing of the child. Children were spoiled, they were seldom corrected and never punished. They did what they liked, and could order the adults to listen to them.

While on an exploration expedition Schaefer (1971) felt that he had deeply hurt an Eskimo father and his little son by tightening the straps, in the son's presence, on the sleigh the son had made ready for departure. The Eskimo father pointed out that, among Eskimoes, it is customary to encourage the child, praise him for whatever he has done and then secretly correct what must be corrected.

The Eskimoes never doubt a statement made by someone else, especially their parents. This is essential in order to acquire the knowledge that makes it possible to survive (Nelson 1969).

Strakats (1965) reported on the traditional upbringing among the nomads of Siberia and pointed out that a characteristic feature among the inhabitants of tundra and taiga is the close relationship between adults and children. Children accompany adults everywhere, are constantly receiving instruction by practical demonstration, and early begin to take part in work. By means of games and competitions in lasso-throwing, spear casting etc., often supervised by adults, they are trained in skills which are later of importance in reindeer herding and in hunting.

By means of the grown-up's stories concerning both the past and the present, the child's sphere of comprehension is widened, and his intellectual talents are trained by riddles and guessing games.

Arctic people show an appreciation of children hardly found in other parts of the world. Boys, in particular, even while quite young, wield a great deal of influence within the family (Palm 1920).

The difference between child and adult in the primitive stage is so small that an equality in the relationship is easy to maintain.

3. *Child rearing among Skolt Lapps*

»The purpose of the Lapps' upbringing is to create physically strong and skilled reindeer herders, hunters and fishermen, and good home makers and housekeepers, who observe the moral duties they have towards other people, and follow the precepts of religion in their way of living. Furthermore, the upbringing must give the individual the stamina that he will require in his life.» This is the definition Päivänsalo (1953) gave of the upbringing of Lapps before the First World War.

Like other research workers, Päivänsalo emphasizes the love for children that is noticeable among the Lapps. He himself observed the good relationship between husband and wife in Suenjel, and the love and tenderness with which Skolt mothers treated their children. Pelto (1962) also saw that both parents often took the babies in their arms, chattered with them and held them during meals. Crying infants are seldom ignored; they are comforted as far as possible, often by oral satisfaction, i.e. by being fed. Older children al-

receive attention from their parents, often in the form of sweets. The parents frequently boast of their children in front of visitors. Up to the age of 2—3 years life is much simpler for the Lapp child than for children growing up in a more complicated culture. The Lapp child does not have to greet people, to say thank you and to sit still, nor does he have to learn complicated table manners or other things which are not considered important among the Lapps.

Lapp children are seldom subjected to corporal punishment. The schoolmistress at Suenjel said that the Skolt children were usually well behaved and obedient, and that she got along well with them. However many Skolts punish their children if they are disobedient. Especially if the children break something at a neighbour's or repeatedly show disobedience, they are punished immediately. A mild measure is to pinch the child's ear but if that does not help the child is whipped with a birch or a strap of reindeer leather (Pälvänsalo 1953).

Anochin (1963) says that the Lapps of the Kola Peninsula are rather strict with their children but never use corporal punishment.

According to Pelto (1962) corporal punishment is most frequently used by Skolt Lapps when they are trying to teach the child to control his aggressions, in other words, in connection with quarrels among the siblings, etc.

Attention has earlier been devoted to the results the Lapps have achieved with what is regarded as permissive upbringing and slack discipline. According to Bernatz (cited by Pälvänsalo 1953) no disobedient children were seen. They showed respect for their parents with whom they lived in friendly relationship. They showed no resistance to the parents' authority and respected the traditions.

In the home the life led in common by both adults and children was in itself educational. The gap that with us is often found between the generations was not so perceptible there, where the adult is a kind of child whose spiritual life is natural and simple, while the children are already small adults.

The reason why the Lapps so seldom use corporal punishment may therefore, depend partly on their love of children, partly on their relatively free upbringing but according to Pälvänsalo (1953), it may also be found in the Lapps' ancient belief that the spirit of an ancestor can be reincarnated in a child. It is natural that the parents do not wish to arouse their ancestors' displeasure by giving the child corporal punishment. Although this ancient belief is no longer consciously held by the Lapps, it is nevertheless possible that the old habits have been retained. Similar situations are known among Eskimoes and other Arctic nomads (Meyer Rochow 1972).

Training for work

Pälvänsalo (1953) describes how the children in Suenjel did the household chores, sawed wood, washed the dishes, made fishing nets, and took part in the tanning of reindeer skins.

The children are encouraged to do these jobs but they are seldom forced, nor are they punished if they refuse. The wish to be grown-up is nurtured in the children, and they are often treated as if they were miniature adults. Positive rewards are frequently used by the Skolts in bringing up their children. A child is not generally pressed to learn things before he is 10 years old. The father is usually the boy's teacher in reindeer herding but gives very little formal instruction, only the main essentials. The boy learns most things by observation and he is never scolded for failure or mistakes. As a result, learning is a source of pleasure, unhurried and with no fear of failure (Pelto 1962).

Since the Lapps move about in vast uninhabited tracts it is important that they should learn to manage in the wilds, to learn to recognize the shape of a fell, stones or a tree, which may later serve as a landmark, and to tell the points of the compass by various signs in nature. »The Skolt children, just like the adults, have a compass in their heads and even the very small children know their immediate surroundings and the tracks of animals» (Pälvänsalo 1953).

In these days the Skolt children are legally bound to go to school from the age of 7 years onwards, and many spend a good part of the year in the school boarding house. As a result, they miss most of the practical learning they earlier used to pick up while accompanying the adults on their journeys. Subjects such as Lapp handicrafts, the Lappish language and culture have only recently been included in the Swedish school schedule, and Lapp material has been integrated in geography, regional study, history and nature study lessons. A special vocational training course of reindeer herding has also been started for the more advanced pupils (Ruong 1969).

Intellectual training

Among primitive people it is possible to manage quite well with a smaller store of theoretical knowledge than among highly civilized nations. For this reason deliberate *training of the intellect is not so important* as the practical training. A certain tendency to exercise the intellect is seen in the Lapps' habit of solving riddles, which especially in earlier times was very popular in Lapland.

Fairy-tales can also be considered to contain an element of intellectual education in that they develop the children's fantasy, promote their adaptation to society and develop their moral values.

Ethical upbringing

In moral issues, the Lapps set great store by honesty, which is a vital necessity for the existence of a nomad population. The parents constantly impress their children with the necessity for honesty and point out that they must not touch anything when they visit other people.

In one respect, however, the Skolt Lapps appear to violate the rules of honesty and that is in the matter of reindeer stealing. It may be assumed that for example, the view that reindeer are half wild may have something to do with this, with the result that stealing reindeer is not considered in the same category as the theft of other property.

In the Skolt community, according to Pelto (1962), great emphasis is laid on developing self-reliance and independence, which the child learns at an early stage thanks to the warm affection, the »basic trust», that the child experiences from the very beginning.

Summary of Skolt upbringing according to the literature

An outstanding feature in the Skolts' upbringing is the atmosphere of relatively great freedom and permissiveness. Children should cooperate with the grown ups of their own free will. Learning must therefore not be forced, and the child's own stage of development must always be observed. Discipline and punishment may sometimes be necessary but they are used sparingly and without aggressiveness (Pelto 1962).

In addition, the upbringing is characterized by a close-knit relationship of parents and child and by the fact that the main emphasis in teaching is on imitation.

4. *Breast feeding and weaning*

Among the so-called primitive people breast feeding is the most practical way of satisfying the child's nutritional needs. According to opinions based on Freud's theories, breast feeding is important for the child's emotional well being and is the best way of satisfying its oral needs. Of greater importance, probably, is the mutual interaction, the emotional atmosphere between mother and child.

Among the Western cultures breast feeding has tended to decrease everywhere. The period of lactation ranges from 0.92 months in Brussels to 4.5 months in Stockholm (Hindley 1968). The Stockholm mothers who breast fed their children longer were usually more assured and calmer and showed a greater self reliance. Boys were breast fed longer than girls, and older mothers (over 26 years) breast fed their babies longer than the younger. Mothers in the higher social groups, and those with a higher educational level breast fed their babies longer than the mothers in the lower social groups and

with only primary school education (Klackenberg and Klackenberg Larsson 1968)

Whiting and Child (1958) attempted to determine the initial satisfactions among primitive people by means of four factors, one of which was the length of the period of lactation The period of lactation is known among 52 racial groups, and only two have periods of less than one year (the shortest period is reported for the Marquesans viz less than 6 months) The Lapps are reported to lactate for 2 years, as did most of the other primitive cultures.

According to Mellbin (1962) about one third of the Lapp children in Sweden were breast fed for six months, one-third between six and 12 months, and one third for more than 12 months. The period of breast feeding in the Northern Lapp district was significantly longer than among the Lapps in the South and in both groups longer than among the Swedish population in general Mellbin ascribes this to the lower social standard among the Lapps, and to their nomadic life where cow's milk was not always available.

The Skolt mothers reported to Pelto (1962) that babies in Suenjel were usually breast fed up to the age of two years but that public health nurses were recommending shorter lactation. Pelto noticed that babies were given the breast when they cried One mother gave her baby the breast four times during the 4 1/2 hour conversation she had with Pelto Sometimes the baby had not even started crying before the mother picked it up

In the Finnish rural districts the usual period of lactation was 18—24 months, but a mother's youngest child might be breast fed up to the age of 7—8 years (Ruoppila 1954) According to Hultin (1973) in a sample of 3600 children from all Finland ca 53 per cent were breast-fed for 3 months or more, 20 per cent for 6 months or more, but none for 9 months, which in 1952 still happened in 31 per cent (Hallman et al. 1959)

Weaning

Comparison of the various cultures shows that the Western culture is practically the only one where weaning begins according to the child's chronological age. Thirty of 106 cultures applied a certain standard of maturity (the cutting of teeth, crawling walking etc.) as the criterion, but in most cultures the mother's pregnancy or the birth of a younger sibling determined the length of the period of breast feeding Weaning and training in independence take place earlier in cultures where the family forms a nucleus with father and children competing for the attention of only one woman (Whiting and Whiting 1966)

Hindley (1968) found, among European mothers, that weaning was more difficult if the children had been breast fed for a long time, and assumed that this was perhaps because the habit of sucking had become more deeply rooted and was therefore more difficult to give up According to Whiting (1963) weaning disturbs the child most if it takes place at the age of 18 months. Before or after that age, it has not the same significance.

Ruoppila (1954) tells that when Finnish mothers were weaning their children they spread their nipples with tar or nicotinic oil taken from a smoked pipe, or stuck tufts of wool on the nipples, or even entirely covered the nipples with fur Some mothers painted their nipples black and said that milk had become black and undrinkable.

Lapp mothers used to rub resin, tar or ashes onto the nipples or even pinch the child's ear when it began to suck. Sometimes the mother went away with the reindeer herds during the period of weaning (Itkonen 1948)

Pelto (1962) wrote that camphor salt or feathers were put on the nipples during weaning in order to reduce the child's interest. Many mothers said that the interest decreased as soon as the baby was given solid food. Milk powder and canned milk were used instead of breast milk earlier reindeer milk had been used

5. *Toilet training*

The attitude towards toilet training varies in different cultures it tends to be stricter in the Western Countries. Whiting

and Child (1958) appraised the toilet training in 22 »primitive» cultures and found that it was exceptionally severe among the Tanal tribe where it was started at the age of three months and the child was expected to be fully trained at six months. After this the child was often punished, even severely, if an accident happened. In half the cultures recorded, toilet training started between 1 1/2 and 2 1/2 years, among the Sena tribe in Africa as late as at five years. A common attitude was that the child had to understand what it all was about and punishment was not often used.

Among the 1428 Sudanese children studied by Cederblad (1968) training started as early as 40 days to two months, with the mother holding her baby in a sitting position between her knees. The child was not punished in the event of an »accident». Sudanese mothers expected the child to be clean and dry at the age of three years. No real training was given to 29 per cent of the children.

Hindley et al. (1968) studied the conditions in five European cities and found considerable differences. In London, for example, training was started early, at the mean age of 4.6 months, in Stockholm the figure, according to Klackenberg (1971), was 12.4 months. Since toilet training, unlike suckling, is independent of the mother's physiological functions, the curve obtained is smoother and follows the logarithm of the child's age. The process correlates with the mother's attitude and the child's response.

According to a study of nearly 2000 Finnish mothers in different parts of the country (Marin 1960), the great majority (66 per cent) started toilet training when the child was 6—12 months old, about 17 per cent at one year, and about 14 per cent before the age of 6 months. Takala (1960), in her study of Finnish mothers, found that toilet training was begun earliest in an urban environment whereas in the distant rural districts it may have taken up to two years before the training was started.

According to Pelto (1962), the general attitude to toilet training among the Skolts is relaxed. The parents do not teach their children any particular aversion towards faeces or urine, and the attitude is much the same as towards clay or hay. The Skolt house is not kept so clean and tidy that the parents would find it important to teach the child to control his bladder or bowels at an unreasonably early age. Most mothers emphasized that it was important for the child to »understand» before training was started, in other words, usually at the age of 1 1/2—2 years. If children over two years could not yet keep clean and dry, this aroused no particular attention. The training therefore is flexible and patient, and there is little chance of the child being »traumatized» or given an anal complex, with a fear of strict discipline, faeces or compulsion or with other manifest reactions. No fear of failure develops, and the training does not inhibit the gradual development of the child's confidence and self reliance.

C. SOMATIC ASPECTS

1. *Physical health*

A high incidence of infections of the respiratory tract and ear infections is reported among Eskimoes, whereas tuberculosis has decreased in the last few decades (Reed et al. 1967).

Infectious diseases are not immunological but are more often due to poor hygiene and a lack of sanitation (Fleshman 1968).

A high incidence of hearing defects following earlier infections has also been shown among Lapp children in North Sweden by Mellbin (1962), who found no active tuberculosis.

Tiisala et al. (1962) estimated the frequency of an increased tendency to infectious diseases among children under the age of 15 years in Finland at 25.8 per cent. The authors point out, however, that the criteria of the assessment were subjective and that comparisons were difficult. No significant differences could be found between the state of health among the children of the southern and northern parts of the country.

2. *Growth*

The mean height of children in Finland has increased since the 1920s, 1930s and

2

with only primary school education (Klackenberg and Klackenberg Larsson 1968.)

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5. *Toilet training*

The attitude towards toilet training varies in different cultures; it tends to be stricter in the Western Countries. Whiting

and Child (1958) appraised the toilet training in 22 »primitive» cultures and found that it was exceptionally severe among the Tanal tribe where it was started at the age of three months and the child was expected to be fully trained at six months. After this the child was often punished, even severely, if an accident happened. In half the cultures recorded, toilet training started between 1 1/2 and 2 1/2 years, among the Sena tribe in Africa as late as at five years. A common attitude was that the child had to understand what it all was about and punishment was not often used.

Among the 1428 Sudanese children studied by Cederblad (1968) training started as early as 40 days to two months, with the mother holding her baby in a sitting position between her knees. The child was not punished in the event of an »accident». Sudanese mothers expected the child to be clean and dry at the age of three years. No real training was given to 29 per cent of the children.

Hindley et al. (1968) studied the conditions in five European cities and found considerable differences. In London for example, training was started early, at the mean age of 4.6 months; in Stockholm the figure, according to Klackenberg (1971), was 12.4 months. Since toilet training, unlike suckling, is independent of the mother's physiological functions, the curve obtained is smoother and follows the logarithm of the child's age. The process correlates with the mother's attitude and the child's response.

According to a study of nearly 2000 Finnish mothers in different parts of the country (Marin 1960), the great majority (66 per cent) started toilet training when the child was 6—12 months old, about 17 per cent at one year and about 14 per cent before the age of 6 months. Takala (1960), in her study of Finnish mothers, found that toilet training was begun earliest in an urban environment whereas in the distant rural districts it may have taken up to two years before the training was started.

According to Pelto (1962), the general attitude to toilet training among the Skolts is relaxed. The parents do not teach their children any particular aversion towards faeces or urine and the attitude is much the same as towards clay or hay. The Skolt house is not kept so clean and tidy that the parents would find it important to teach the child to control his bladder or bowels at an unreasonably early age. Most mothers emphasized that it was important for the child to »understand» before training was started, in other words, usually at the age of 1 1/2—2 years. If children over two years could not yet keep clean and dry, this aroused no particular attention. The training, therefore, is flexible and patient, and there is little chance of the child being »traumatized» or given an anal complex, with a fear of strict discipline, faeces or compulsion, or with other manifest reactions. No fear of failure develops, and the training does not inhibit the gradual development of the child's confidence and self reliance.

C. SOMATIC ASPECTS

1 Physical health

A high incidence of infections of the respiratory tract and ear infections is reported among Eskimoes, whereas tuberculosis has decreased in the last few decades (Reed et al 1967).

Infectious diseases are not immunological but are more often due to poor hygiene and a lack of sanitation (Fleshman 1968).

A high incidence of hearing defects following earlier infections has also been shown among Lapp children in North Sweden by Mellbin (1962), who found no active tuberculosis.

Tiisala et al (1962) estimated the frequency of an increased tendency to infectious diseases among children under the age of 15 years in Finland at 25.8 per cent. The authors point out, however, that the criteria of the assessment were subjective and that comparisons were difficult. No significant differences could be found between the state of health among the children of the southern and northern parts of the country.

2 Growth

The mean height of children in Finland has increased since the 1920s, 1930s and

1940s (Takkunen 1962, Bäckström Järvinen 1964) According to Mellbin (1962) the mean height curve for the Lapp children in North Sweden shows an increase. The increase is greatest in the northernmost parts. This is interpreted by Mellbin to be a result of the environmental changes, which have taken place more rapidly in the North, whereas the other districts already had a higher standard of living earlier The influence of environment on growth and development, according to his opinion, takes place before the age of seven apparently in the very earliest years of life The boarding school environment did not affect the development of height and weight.

3 Psychomotor development

Apart from the wellknown studies by Gesell, few systematic studies have been made of the genetic development of the motor processes. Most studies concerned with the child's psychomotor development have dealt with the first walking Many authors (Knoblock and Pasamanick, Williams and Scott, Geber cited by Hindley et al. 1968) are of the opinion that the age of first walking is not, as was believed before, dependent on race but rather on socioeconomic and especially cultural factors. Hindley and his fellow workers (1968) studied the age at which groups of children in five European countries took their first steps, but found no differences relating to sex or social group They do however think it possible that environmental factors, such as nutrition and maternal attitude, could be of importance It is also suggested that genetic differences could possibly play a part In the material published by Salo (1947) the date at which 717 Finnish children first walked alone was definitely known. The mean age for boys was 11 months 25 days and for girls 11 months 19 days Of 189 children in Salo's material, the majority sat at the age of 7 months

The literature on the child's speech development is comprehensive McCarthy 1966) gives a survey of the literature in which she among other things, determines the age for the first word as 11 months, on the basis of data collected from the literature Salo (1947) has compiled data concerning the first word uttered by 3318 Finnish children. According to these, most children begin to speak at the age of 12 months, many at 13 months The range of the ages at which children begin to use meaningful words is, according to Salo 9—15 months

Adequate motor test scores have been difficult to set up One of the oldest yet seldom applied is the scale of Oseretsky's motor test. Lassner (1948) published a review of the literature on this scale. Endeavours to correlate motor skills with mental and physical development have been made e.g by Espenschade (1940) who found that the motor development of boys in puberty correlated with chronological, emotional and physiological signs of maturation, whereas such a correlation among the girls was low According to Sloan (1955) motor skills are related to general intelligence. He stresses, however that motor skills are relatively specific, and that little correlation can be traced between individuals in a study group unless the same group of muscles is involved

Correlation with physical development and gross motor skills but not with mental development was found by Govatos (1959)

D INTELLECTUAL FUNCTIONS

The complex nature of intelligence is generally recognized, and fundamental studies to investigate it have been published e.g by Spearman Thurstone and Guilford. The last mentioned points out that the dissimilarities noted between the test results for the various races primarily reflect the dissimilarities in the potential development of the particular skills in the cultures in which the individuals live and have grown up

Vernon (1965) takes up the idea of genetic differences between races or ethnic groups but says that, in accordance with the UNESCO declaration he believes that they cannot be proved and that in any case they are apparently small compared with the differences arising from the environment. He points out how the

various components of intelligence largely depend on personality and motivational factors, organic and social drives, curiosity and interests, and how they are formed by family cultural and educational pressures. Intelligence, therefore, depends on the totality of the skills and techniques of mastering problems, crystallized from the child's earlier experiences

Vernon lists nine factors in the environment which, according to various studies, have been found to be a handicap for mental development Among them are nutritional factors, mistakes in the upbringing such as repression of independence and constructive play maternal dominance and too little paternal participation in the upbringing leading to the lack of a masculine identification object, actual privation and insecurity of livelihood a lack of school education, and linguistic handicaps both as regards bilingualism and subcultural differences in districts with a single language.

Anastasi (1966) discusses the problem of testing children who have grown up in different cultures or subcultures. She points out that a test always tends to favour the culture in which it has been construed. According to her there is no test that would be unrestricted in its cultural reference, and the difference between the »culture-free» and »culture bound» tests would only be a difference in degree

Mental deficiency

Although it is generally recognized that mental retardation is not only a manifestation of defective intelligence but also largely a result of factors such as social adaptation and emotional balance the grading based on intelligence quotient still is and remains the most utilizable in practice. According to the WHO standards, those with an IQ under 68 are reckoned to be mentally subnormal (Classificatio Morborum et Causarum Mortis 1969)

Epidemiologic studies of mental deficiency have been made in Finland e.g. by Kalla (1942) and Amnell (1964) According to the former the rate of idiocy and imbecility is 4 43 per mill, and according to Amnell et al. who by the census method selected and examined 4013 individuals using e.g the KTK test (according to Elonen et al. 1963) the rate of grave mental retardation was 3 65 per mill and slight retardation 2.97 per mill. The latter rate however is considered too low by the author himself.

E. PSYCHOSOMATIC AND NERVOUS SYMPTOMS

1 *Sleeping disturbances*

It is difficult to register disturbances in the sleep objectively since much depends on the mother's own sleep and her sensitivity to the phenomenon According to Klackenberg (1971) waking at the age of 4—5 years should not always be attributed to nervous disturbances, but should rather be classified among the physiological variations in the depth of sleep He points out that one in every ten 7 years old has somnambulism According to Wurst (cited by Cederblad 1968) sleeping disorders decline with a large number of siblings. This observation was also reported by Gedda (1953) and it can be taken to mean that several siblings give a greater sense of security during the night. No correlation has been shown between the standard of housing and disturbed sleep (Gottfarb et al. 1963) In Stockholm, 14 per cent of the boys have sleeping difficulties (Jonsson and Kälvesten 1964)

The frequency of sleeping difficulties in the Sudanese material of 1716 children published by Cederblad (1968) was only 3 per cent, and even then the disturbances never occurred alone but were linked up with troubles such as enuresis, aggressiveness and anxiety and phobias such as fear of the dark. Among 2391 children in their first year at school in Hamburg v. Harnack (1953) found 16 4 per cent with restless sleep and 5.9 per cent with night terror and somnambulism

2 *Headache*

v. Harnack (1953) found headache in 23 1 per cent of Hamburg school children aged 10—11 years, against 15 7 per cent among other children. He studied 2400

children in their first year at school and found recurrent headache in 5 per cent (56 per cent of these had slight symptoms) No correlation between pathologic environment and headache could be shown except for noise among children living in the centre of the city Jonsson and Kälvesten (1964) observed headache in 17 per cent of 222 Stockholm boys of ages ranging from 7 to 15 years. Bille (1962) studied school children aged 7—15 years in an urban milieu and found that 48 per cent had headache seldom, 5.8 per cent often, and another 3.9 per cent had migraine.

Cederblad (1968) among the 1569 Sudanese children of the age range 3—15 years studied, found headache in 4 per cent. Headache was the only symptom in 64 per cent of the cases otherwise it was usually combined with phobias, anxiety and depression.

3 Poor appetite

Shirley (1963) reports that in the 1940s in well-regulated and economically and educationally priviliged homes the »anorexia» of childhood was so common that it could almost be looked upon — although it was not — as normal, and it was largely iatrogenic in origin the child's reaction to an overanxious mothers attempt to follow a rigid dietary prescription. In his studies v Harnack (1953) found that 20.4 per cent of the children in the first year of school had a poor appetite. In 5 per cent the symptom was pronounced. The symptom was more often present in girls and in children of the upper social group

The incidence of anorexia among Stockholm boys aged 8—15 years was 4.5 per cent (Jonsson and Kälvesten 1964) According to Macfarlane (1954) the incidence is about 20 per cent, with the emphasis on girls. In Cederblad's (1968) material there was no difference between boys and girls and the incidence was 1 per cent. In Finland, about 25 per cent of the mothers of preschool age children complain of their children's poor appetite this was the outcome of a study by the Mannerheim League for Child Welfare

The fact that anorexia is a phenomenon belonging to the welfare society has been stressed by Brenneman (1938) Annell (1959) and Kanner (1962) and by v Harnack (1953) who points out that a lack of appreciation of food, alone, affords the possibility of symptom formation, but manifest anorexia is not involved until unfavourable environmental factors are added.

4 Abdominal pain

Little information is available in the literature on recurrent abdominal pain that can be interpreted as psychogenic. Apley (1967) stated that 10 per cent of all children have such pains at some time during their lives.

5 Enuresis

As pointed out above (p 17) different cultures have different opinions concerning the age at which toilet training should be started. For this reason, various studies give different information on the age at which the major part of the population is dry The ability to retain urine is a function that depends on the child's age, and involuntary discharge of urine after a certain stage of maturity is considered as enuresis Enuresis nocturna is more frequent than enuresis diurna which only occurs in 5 % of the cases Only nocturnal enuresis is discussed in the following According to most studies, 25 % of the 3-year olds are still bed-wetters. Hägglund (1966) states that 10 % of 7 year old primary school children are bed-wetters, while Hallgren (1957) quotes 6.6 % for school beginners and Bellman (1966) 5.8 %. These authors studied urban dwellers.

Klackenberg (1971) on his material of 245 children, found that 14 % had nocturnal enuresis at the age of 4 years and 6.6 % still at the age of 7

Among the Sudanese children studied by Cederblad (1968) the total rate of enuresis was 13.7 % at ages ranging from 3 to 15 years. For children aged 7 to 15 years the frequency had sunk to 8 % but it was significantly higher among the boys (21 %) than among the girls (5 %)

Hallgren (1957) finds the etiology of enuresis heterogeneous there are »non

genetic» cases but most probably also a »hard core» of cases which are primarily genetically dependent however the degree and manifestation of the genes is determined by environmental factors. Furthermore, he traced a relationship between enuresis and other »regressive symptoms» such as emotional immaturity and speech disorders but not with dyslexia.

v Harnack (1953) found a larger number of severely enuretic children among families of the lower social groups and ascribes this to the poorer housing conditions, lower nutritional standard, and other adverse conditions accompanying economic difficulties

6 Encopresis

According to the generally accepted definition, encopresis means the involuntary discharge of faeces in cases where the incontinence is not due to anatomical anomalies or other organic defects.

The ability to control the bowel function depends on the child s neurophysiological maturity which varies from one individual to another According to Klackenberg (1971) the girls of his study had achieved control at a mean age of 20 months and the boys at 25 7 months

As for enuresis the definition of encopresis is in keeping with the cleanliness requirements of each individual culture and subculture. The standards according to which a child should be considered encopretic vary among the different investigators. According to Lomholt (1965) no encopresis is involved until the child is 3 years old. Jonsson and Kälvesten (1964) place the limit as high as at 6 years while Bellman (1966) places it at 4 years.

Bellman quotes a rate of encopresis of 1.5 for a Swedish material with a mean age of 7 3/4 years. The longitudinal study by Klackenberg (1971) gave a frequency of 3 , at the age of both 7 years and 8 years (200 children)

Among the Sudanese children studied by Cederblad (1968) the rate of encopresis was only 1 4 % among the boys and 0 7 % among the girls in the age bracket of 3—15 years in the total material of 1716 children. Not one girl over 6 or boy over 11 years had the symptom.

7 Thumb-sucking

A moderate degree of finger-sucking often thumb-sucking is considered common in infancy and early childhood.

According to psychoanalysts, pronounced finger sucking is a manifestation of an unsatisfied need during the oral phase of development. In the first half of this century thumb-sucking was widely held to be a sign of psychic disharmony but in the last few decades it has been more generally considered as a harmless bad habit, or rather a habit by means of which the individual obtains relaxation and satisfaction. Klackenberg (1971) found, among other things, that thumb-suckers who had had the habit for at least five years showed no more symptoms of nervous disturbance than the non-suckers (disturbances of sleep or speech, food problems, etc.) The only significant difference he found was that the non-suckers had a higher percentage of mothers in gainful employment outside the home even though thumb-sucking has, by many been considered a sign of inner tension. According to Klackenberg (1971) the frequency of thumb-sucking falls slowly after the age of 18 months, and 60 % of the children who suck at this age still suck their fingers at the age of 8, that is to say about 20 % of all 8-year old children.

According to the learning theory which has recently gained ground finger-sucking could be considered an acquired process depending on the original agreeable association with feeding and nursing (Benjamin, cited by Klackenberg 1971)

Breast feeding over a long period might, therefore, predispose to thumb-sucking both according to the psychoanalytic theory — overgratification and fixation (Yarrow 1954) — and the learning theory However the length of the breast feeding period is an inadequate criterion of the satisfaction of the need for sucking since most children have subsequently been given milk from a bottle and the sucking has thus been continued. According to Klackenberg (1971) up to the age

three years the number of thumb-suckers is the same, irrespective of whether the child has been breast-fed or bottle-fed in infancy

Children who were weaned from both bottle and breast before the age of 9 months showed a higher rate of thumb-sucking than those weaned before the age of 12 months (Klackenberg 1971)

Among 1569 Sudanese children aged 3—15 years, Cederblad (1968) found that 1 % were thumb-suckers, 90 % of whom showed anxiety v Harnack (1953) found that 13.3 % of the children in their first year of school in Hamburg were thumb-suckers, a significant majority being girls (Cederblad also has a majority of girls in her series)

From a material of 428 children aged 6—12 years, Lapouse and Monk (1964) reported thumb-sucking in 10 per cent, of whom every fifth was sucking »almost all the time»

8 Nail-biting

In the literature, nail-biting is usually considered a sign of inner tension and restlessness (Kanner 1950) or an adequate tension-relieving reaction (Homburger cited by v Harnack (1953)

Jonsson and Kälvesten (1964) who studied Stockholm boys aged 8—16 years, reported nail-biting in 20.8 %, v Harnack (1953) in 16.1 of the children in their first year of school in Hamburg Cederblad (1968) in 2 of children aged 3—5 years in Sudan. It was an isolated symptom in 40 of Cederblad's material, but otherwise was most often combined with anxiety

Wechsler (cited by Klackenberg 1971) found that 36 % of the 3000 school children he studied were nail-biters, and Gedda (1953) quoted the figure of 7 for 7 year old girls.

According to Klackenberg (1971) the symptom varies in one and the same individual and can recur after long periods of absence. In his material, 5 of those who began school were permanent and 15 occasional nail-biters while almost 40 bit their nails rarely The percentages were significantly higher for girls than boys. No correlation was noted between beginning school and finger-sucking and/or nail-biting There was a slight tendency that the mothers usually characterized nail-biters as more defiant.

Lapouse and Monk (1964) showed nail-biting in 27 % of their material of 428 children aged 6—12 years. 17 % of the children had badly bitten their nails.

9 Motor restlessness and hyperactivity

Hyperactivity and lack of concentration are often considered manifestations of a more or less marked degree of brain damage. Chess (1969) however utters a warning against assuming that all hypermotor children are brain injured. She found that of 89 brain-damaged children, approximately half showed hyperactivity and many of these were aggressive. But the series also contained children who were neither hyperactive nor aggressive.

v Harnack (1953) in his study of 2391 children, characterized 10.3 as moderately restless, and 11.8 as markedly restless (with boys somewhat in the majority) The probability that a »nervous» mother has a hypermotor child is 1 2.6 which is greater than the probability for a calm mother 1 10

According to Jonsson and Kälvesten (1964) 5 % of Stockholm boys were considered hyperactive by their mothers. The authors emphasize that this largely depends on the mothers attitude, and their tolerance for the symptom. Macfarlane et al. (1954) found that hyperactivity was most common in the late preschool age (45 % among boys and 35 % among girls aged 4—5 years) Up to the age of 14 years, the frequency of disturbing hyperactivity in their material was slighty less than one-third of all the boys.

10 Aggressive outbursts

Aggressive outbursts, especially in the preschool age, may be regarded as the child's defence in stress situations. They are common in early childhood and should not make the parents apprehensive Shirley 1963)

According to v. Harnack (1953) out bursts of defiance and rage occurred in 59% of children in the first year of school.

Macfarlane et al. (1954) report that the rate of open aggressiveness among both boys and girls up to the age of 14 is 44%.

Klackenberg (1971) found that over *half of the children who at the age of 4* years have daily temper tantrums will later have similar reactions from time to time though less frequently. He draws the conclusion that temper tantrums at the age of 7—8 years have a slightly more distinct significance than at the age of 3—4 years.

Cederblad (1968) found deviant aggressiveness, open and suppressed in 18% of her series of Sudanese children aged 3—15 years. Open aggressiveness was most frequent among boys, and in the younger age group.

II Fear

»The word fear, though also a general term, is often used to designate particulary the more or less acute emotional reaction to a specific, actual, outside danger. Anxiety is the word commonly used to denote a persistent or chronic fear, especially one which results when the individual faces the unknown or a new situation which may present potential hazards.» (Shirley 1963)

Many other attempts have been made to differentiate between fear and anxiety. It is usually considered that the feeling of danger in the event of anxiety is internal and subjective. The psychoanalytic opinion that anxiety is a product of suppressed aggressiveness and animosity is well-*known but also many other conflict* situations and impulses, unfulfilled needs and ambitions, obligations, »oughts» and »shoulds» underlie anxiety (Jersild 1966). According to Horney (1968) anxiety is the result of disturbed relations which the individual finds vital for his security; a feeling of isolation and rejection leads to helplessness, fear and animosity, which represent the individual's ways of coping with the world in spite of the underlying feeling of anxiety.

Sinha (1962) tries to clarify the role of culture in the development of anxiety and points out that cultural factors operate in two ways: by engendering predisposition for anxiety and by providing possible occasions for anxiety reactions. Culture can be considered to predispose to anxiety through certain patterns in the family constellation, child rearing, belief in authority etc., factors that can create *a personality who feels inadequate, weak,* lonely, anxious and uncertain.

Western culture represents a »competitive society» where the middle class in particular constantly strives to reach a better »status». This is considered by many to predispose to anxiety reactions (Kardiner 1945 and others).

Different cultures afford different opportunities of anxiety reactions. As a contrast to the competitive industrial society Sinha (1962) describes an Indian tribe, the Saulteux, who have a strongly positive attitude towards long life and health and consider illness a punishment for earlier evil deeds. An illness therefore creates strong neurotic anxiety.

Sinha emphasizes further that a western influence confuses the standards of child rearing and traditional family patterns in an Indian culture and so creates the possibility of anxiety reactions. Uncertainty and anxiety, especially among the young people, is produced by a transition from the early childhood with their parents' permissive attitude to a society with stricter standards, rigid codes and fewer signs of permissiveness.

Anxiety is thus also a condition in *which the individual finds it difficult to* explain to himself what he is afraid of; the reason for his fear is diffuse and obscure. *On the other hand, in the event of fear,* the feeling is often more clearly recognized as fear and the individual apprehends the threatening situation.

Anxiety can also be manifested in the form of phobia. Phobia is defined as an obsessive, persistent, unrealistic fear of an external object or a situation. It is assumed to arise from an internal conflict projected outward onto an object which is symbolically related to the fear (Jersild 1966).

Especially with children it may be extremely difficult to distinguish between »phobia» and »fear», the more so since

children tend to attach their anxiety to an object (v Harnack 1953) Jersild (1966) describes how in his study of young school children, there was a great discrepancy between the object of the children's fear and the actual danger situations they had experienced. For example 14 % said they were afraid of animals while only 2 % had really been attacked by an animal According to him, such »irrational fear» occurs early in childhood, and it is appar ently normal for a child to have irrational fears which *should not be designated* as signs of intrapsychic conflicts or neurosis

In his study of 2391 children aged 6—7 years, v Harnack (1953) classified child ren with 3—4 objects of fear as »very an xious» (5 8 %) and those with 1—2 objects as »moderately or slightly an xious» (29 7 %) The most common objects of fear were fear of the dark, (43 7 %) of being left alone (39 3 %) burglars, robbers, murderers (11 6 %) other objects such as Father Christmas, ghosts witches, war bombs had a fre quency of less than 2 %

Cederblad (1968) reported a 12 % rate of phobias among Sudanese children aged 3—15 years while the mothers of her study reported anxiety in 13 % How ever the difference between phobia and anxiety is not clear Fear of the dark was noted in 70 %

According to Croake (1969) earlier authors have often shown that girls list a larger number of objects of fear than boys, as do children of a lower socioeconomic standing compared with those of a higher standing which also was the result of his own investigation Furthermore, children under 4 years are reported usually to be afraid of noise and situations connected with noise. Fear of animal was recorded as the most common fear in 5- and 6-year olds. This was the case also with the 7 and 8-year olds, who additionally had fears of supernatural events and beings, and concerning their own safety From age eight to adolescense in the studies reported by Croake *there was no unanimous agree ment* as to the most prevalent types of fears. The most frequently mentioned were supernatural beings, the school, physical injury punishment, and animals.

n the study of 482 children by Lapouse and Monk (1959) 43 % had seven or more objects of fear of the 30 that were suggested (children aged 6—12 years)

The most common causes of fear were using somebody else s glass or china 49 % snakes 44 % illness of a family member 41 % thunder 38 % wounds and bruises 38 % school reports 38 % the dark 24 % their own illness or death 16 % animals 12 %

No distinct correlation was noted be tween other nervous symptoms and fear nor was it found that an anxious mother was more likely to have an anxious child There was a lack of correlation with the mothers reports in that the mothers reported no fear in 41 % of the cases in which the children said they had fears

Subjects and method of investigation

1 The plan of investigation

Population-genetic studies of the Skolt Lapps were started at Sevettijärvi in 1966 supported, in part, by WHO They were mainly concerned with blood groups, the PTC test and ophthalmo-genetic examinations supplemented by a clinical health examination (Henrik Forsius et al. 1968) The Skolt studies were continued in 1967 and were incorporated in an Inter-Nordic Human Adaptability (HA) Project within the framework of the International Biological Programme (IBP) with child psychiatric studies included in the programme

In August-September 1967 practically all the 1/1 Skolt children i.e. children whose parents were both pure Skolt Lapps, under 15 years of age were examined in the district of Nellim, and also the 1/2 Skolt children, i.e. those with a 1/1 Skolt mother and a Finnish father The examination should be regarded primarily as a pilot study for the purpose of finding out the most suitable methods.*)

The following year in August-September 1968 the studies of the pediatric group continued in the Sevettijärvi district. Here, too all but one of the Skolt children under 15 years of age were examined **)

2 Subjects

The study comprised all the 1/1 Skolt families in Sevettijärvi and Nellim with children under 15 and in Nellim also the 1/2 Skolt families with a Skolt mother and a Finnish father There were, altogether 37 1/1 Skolt and 13 1/2 Skolt families.

The number and sex distribution of the children examined is presented in Table 1 their mean ages in Table 2, and age distribution in Fig 4 The total of the parents interviewed is shown in Table 1 and their mean ages in Table 2.

With the exception of one of the Sevettijärvi children, a boy born 1962 who lived in a children's home (a C. P child) all the 1/1 and 1/2 Skolt children were examined.

The mothers of two of the 28 Sevettijärvi families had died The father of one of the families was also dead and that of the other family had remarried and moved to another place He did not look after the two examined children who lived with their maternal grandmother Three Sevettijärvi fathers were not available for an interview

The nine 1/1 Skolt families of Nellim included one where both father and mother had died, and the children were in the charge of the maternal grandmother Two fathers avoided being interviewed. All the Skolt mothers of the 13 1/2 Skolt families of Nellim were interviewed Four Finnish fathers in Nellim came to be examined on their own initiative and one father had died In this connection no attempt was made to interview the remaining eight Finnish fathers

The mean number of children per family can be seen from Table 3 which also includes the unexamined children older than 15 years of age.

During the life-time of the children included in the material, four infants among the Sevettijärvi families had died

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*) The child psychiatric examination was carried out by the present author the pediatric by Laina Louekari, M. D and the psychological examination by Leila Seitamo, Cand. of Educ. Sc.

**) The same team as above, complemented by Raili Karjalainen, B. A., who assisted the psychological examinations.

TABLE 1

Number of examined children and parents

Place	Sevettijärvi		Nellim 1/1 Skolt		Nellim 1/2 Skolt		Sammali		Tanhua Finnish		Total	
Number of examined children	boys 57	girls 56	boys 17	girls 14	boys 23	girls 21	boys 18	girls 32	boys 30	girls 30	boys 145	girls 153
Total	113		31		44		50		60		298	
Number of interviewed												
mothers	26		8		13		12		15		74	
fathers	23		6		4 (Finnish)		8		14		55	
Number of families	28		9		13		12		18		78	

TABLE 2

Mean ages of examined children and parents

	Sevettijärvi	Nellim 1/1 Skolt	Nellim 1/2 Skolt	Sammali	Tanhua Finnish	Total
Children						
Boys	9.3	9.9	8.0	9.0	8.9	9.0
S.D	3.8	3.1	4.0	4.9	3.3	
Girls	8.5	10.8	7.2	7.7	7.8	8.3
S.D	3.8	3.1	4.1	4.0	3.7	
Mothers	41.4	43.1	35.1	40.9	38.8	39.8
S.D.	9.6	7.2	7.2	7.1	7.4	
Fathers	47.5	51.9	36.3	44.7	42.4	44.7
S.D	11.2	6.6	7.9	7.1	8.0	

TABLE 3

Number of children per family

	Sevettijärvi	Nellim 1/1 Skolt	Nellim 1/2 Skolt	Sammali	Tanhua Finnish	Total
Mean number of children	5.4	5.2	2.5	4.8	4.1	4.6
S. D	2.9	1.6	1.9	1.9	2.6	2.6

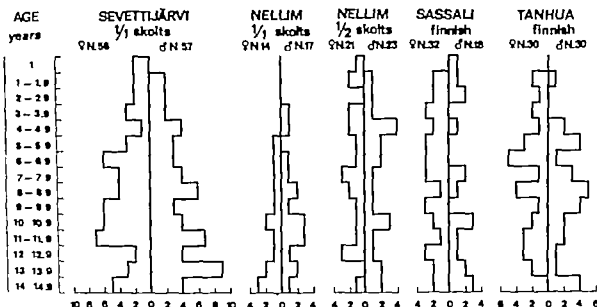


Fig 4 Age distribution of the examined children

at birth, and four children had died at an early age. During the same period of time, there was no instance of a child's death among the 1/1 and 1/2 Skolts of Nellim.

The control group

The intention was to investigate whether the Skolt Lapps special culture affects the children's somatic and psychic health and whether perhaps certain genetic aptitudes could be discovered among them. It was therefore necessary to select a control group of children whose external conditions of life were as similar as possible to those of the Skolt children.

The northernmost places where a more or less homogeneous Finnish population has lived for some time are roughly on the same latitude as the main village of Sodankylä. In the village of Sassali (Fig 1) there is a population group within which the families are closely interrelated. This group had also lived in relative isolation both geographically and ethnically. In the district of Tanhua, in Savukoski community (Fig 1) the scattered population has long lived in geographical isolation, and a boarding school is maintained owing to the long distances. In both districts the people obtain a part of their subsistence from reindeer herding. In the village of Sassali, all families with children under 15 years of age were referred to the control group, provided the parents themselves were definitely of North Finnish origin. These families numbered 12

In the same way 16 families were selected in the village of Tanhua. 102 children of these villages were examined in the summer of 1969 (Table 1) *) A Finnish boy born 1962, lived in an establishment for the mentally retarded, and a boy of 14 from the Sassali village, was harvesting in another locality. All the Sassali mothers were examined. Owing to the busy harvesting season, four fathers could not be seen. In the village of Tanhua, one mother was repeatedly not available for interview owing to adverse circumstances. Two fathers were working in another locality.

The total number of children examined and parents interviewed and their mean ages can be seen from Tables 1 and 2 and age distribution from Fig 4. The mean

*) The pediatric examinations were carried out by Liisa Vesa, M.D. and the psychological tests by Leila Seitamo, Cand. of Ed. Sc., assisted by Leena Kava, B.A.
Child psychiatric examinations were carried out by the present author

number of children per family appears from Table 3. One child in the Sassali group had died at birth during the life time of the children included in the material.

3. Methods

The examinations were carried out in the boarding schools of Nellim and Sevettijärvi. Transport was provided to fetch the subjects from their homes. On arrival, they were often prepared to spend the whole day in the school house, and they had their meals there together with the research workers.

Home visits were also made to the most distant homes to find a child or an adult who for some reason had failed to attend the examination. The author has personally visited about half of the 50 1/1 or 1/2 Skolt homes.

In the Finnish villages the children were also examined and the parents interviewed in the school houses, partly during the summer holidays and partly while the school term was going on. The parents often came to the school for interviews, bringing with them the smaller children who did not yet go to school but even so the author personally went to most of the homes.

Interview with the parents

The parents were interviewed by the present author using the so-called semi open interview techniques, mostly individually but sometimes together. Particularly in the few cases in which an older Skolt mother was not fully proficient in Finnish she was interviewed together with the father who could complement the replies, since the men's linguistic proficiency was usually better *). The questions were concerned with the mothers health during pregnancy, the delivery, breast feeding, the child's development, feeding habits, sleeping habits, behaviour and the parent's views on the child's temperament and psychic health.

The general principles of child rearing were discussed including e.g. toilet training and the use of corporal or other punishment, which of the parents was responsible for the child's upbringing, the child's attachment to the parents, and whether sex information was given.

The parents were asked about their own background, school and upbringing in their childhood home, the situation in their own home and their relationship to the marriage partner.

On the basis of the interview which took 1 1/2—3 hours, and the observations made, a psychiatric assessment was made of the parents. The attitude of the mothers and fathers to the child was appraised separately and graded as warm, neutral, *indifferent or overprotective.*

Health cards

The information given by the parents was checked against that recorded on the children's health cards and kept by the public health nurse at the Child Health Centres. There had been public health nurses in all the villages since the 1950s and detailed data was therefore available for most children on birth weight, the duration of breast feeding, the time at which the child began to sit, walk and talk, all recorded at follow-up visits. These cards and, for the bigger children, the school health cards carried information on illnesses, nutritional status, height and weight. The cards of the Maternity Clinic often described the mother's attitude to the expected child during pregnancy.

Child psychiatric examination

The child psychiatric examination was carried out by the present author in the form of a general child psychiatric investigation and observation.

The children were observed at the examination during free play with various toys, dolls, cars, animals, cooking utensils, coffee sets, toy pistols, etc. The children were also given the opportunity to draw, paint and model.

With bigger children aged over 7 an unstructured interview was made.

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*) Usually, however, there were no language difficulties with the adult Skolts.

In addition, there were occasions when the children could be observed alone and in groups, and together with their parents, while they were waiting for their turn to be examined during the meals, during the breaks on the school yard etc.

A tentative neurologic appraisal of all children was carried out by the author and this was complemented with Oseretsky's motor test on primary school children aged 8—12 years. Instructions and standards for the appraisal outlined by the Institute of Psychology University of Jyväskylä were used.

Behaviour and the degree of cooperation at all these occasions were noted down. A three step grading was used for cooperation: cooperative, neutral, negative.

Psychological examinations

The bigger Skolt children of school age were as proficient in Finnish as in Skolt Lappish whereas an interpreter was sometimes required with preschool-age children. The following special child psychological tests were carried out:

- Intelligence test according to Terman—Merril—Lehtovaara (standardized for Finnish conditions) was used for the preschool-age children, and that according to WISC (Wechsler Intelligence Scale for Children) for the school age children.
- Performance Scale of Educational Research Center of University of Jyväskylä (KTK): two subtests: Stencil Design and Kohs-Häkkinen Cube test were used both the form for the preschool-age children and for the bigger children.
- Goodenough's Draw-a man test and Bender's Visuomotor Gestalt test were carried out on school children.
- Projective tests: the Rorschach test, Children's Apperception Test (CAT) Thematic Apperception Test (TAT), »Children's Reports of Parental Behaviour» (modified after E. S. Schaefer)

Somatic examinations

The clinical examination comprised the following: general condition, height and weight, nutritional status, posture, possible *malformations*, *tonsils*, *jugular* glands, dental status.*)

Laboratory tests: urine with Albustix and Clinistix, haemoglobin according to Sahli and ESR.

4. *Discussion of the methods*

In judging the reliability of the data collected, the value of information supplied by the parents must be very critically assessed, especially that of mothers on the development and diseases of bigger children. According to Pyles et al. (1935) maternal information is very uncertain except as regards birthweight, and erroneous data on the child's health and the mother's own health during pregnancy can be noted as early as 21 months after delivery. Chess et al. (1953) also found that, in one third of the cases, significant differences in the mothers' reports concerning the child's development and the relevant problems were noticeable in the course of a few years.

In most cases the information supplied by the mother could be checked against the data of the health cards. Where differences were noted between the data of the card and those supplied by the mother the former were considered correct since they had been recorded at the time concerned. Deviations between the data, if any, were usually of minor importance. Problems in which the parents' attitude could not be checked by additional questions or other methods were not included in the present study. One of these was the question of the child's sexual behaviour which in itself is important. Problems such as masturbation were not treated since a few test interviews showed that the replies, despite a good contact with the mother, were too vague to serve as a basis for appraisal.

The classification of the parents' attitude is based on the present author's subjective judgment. The examination situation was to serve as basis for the evaluation

*) Dental status was examinated at Sevettijärvi and Nellim by P. Kirveskari, Lic. Odont.

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of the parents attitude. In such a situation errors concerning the individual child are naturally possible in that the parents attitude to a child with a lower parity number would have been quite different during the years of growth or in that the parents attitude has retrospectively changed

The interview with the parents was primarily to be considered as something between an ethnographic interview and a child psychiatric medical history According to Rawnsley (1961) although the interview is less objective and less standardized than a questionnaire, it gives better results and is better received by the respondent.

To establish a better contact with the parents and not to be regarded by them as an authority or one condemning their methods of upbringing the present author used to open the discussion by telling the parents that we who lived in the towns and cities of the more southern regions often had problems with our children and adolescents and wondered whether we could learn something from those being interviewed

The fact that the same person the present author did all the interviewing means that the appraisal of the parents and their attitude is relatively homogeneous Further discussions were held with the local public health nurse who is usually well acquainted with the families in her district

Interviews with children have gained more ground and acceptance in science, and can give good results The weakness is that such an interview is temporary in character and is different at different times and with different interviewers (Yarrow 1966 Anderson 1966) The latter drawback was eliminated in this study since the present author personally carried out all the interviews

The examiner s relationship to the examined is a personal relationship which contributes t the validity of many examination data, and the non-verbal communication during the interview is an important upplement. Children conceal their feeling much less than adults. The child s ability to cooperate with a stranger can be systematically observed in a controlled interview (Yarrow 1966)

Oseretsky s motor test has been criticized e.g by Sloan (1955) who finds that the test describes more the motor activity than the actual components of the motor skills, and should be considered mainly a score of motor development which includes both maturity factors and acquired factors According to Anastasi (1961) however analysis of the test has shown a general factor that could be identified as motor development.

There were no other suitable standardized tests available for the measurement of motor skills at the time the field work was carried out. Oseretsky s test had been used and modified at the Jyväskylä University and also by the present author in earlier examinations (1959) For these reasons it was included in the present battery of tests since it was considered important to find out the extent to which biological and cultural factors affect motor ability The result in any case provides a basis for comparing the Skolt group and the control group regardless of the functions which the test ultimately measured.

5. *Statistical methods*

The tables usually quote the frequencies both in terms of absolute figures (N) and percentages (%) separately for the non assimilated Skolts of Sevettijärvi and Nellim (1/1 Skolts) for those assimilated with Finns (1/2 Skolts) and for the Finnish children in Sasmali and Tanhua respectively

Frequency comparisons were usually made by means of the x^2 method The chi square coefficient (x^2) and degree of freedom (D F) are quoted Mean values were compared by means of the t test and the standard deviation (S D) is also quoted

The result was termed as significant if $p \leq 0.05$ which implies that the level of confidence is ≥ 95 %

The calculations were carried out on a Honeywell 1642 computer and the SURVO-system was used.

Results

A. SOCIOLOGICAL CONDITIONS

1 The Skolt community and the Finnish community

At the time of the examination, the Skolt community at Sevettijärvi was characterized by isolation low economic standing, (Siuruainen 1973) lack of school education among the adults, small chances of gainful employment, and the resulting low motivation for school and education Cultural deprivation was prominent. The Orthodox religion hardly affected them at all, except when the religious festivals came round, a few times a year The dwellings were small and cold (Pelto 1973 Siuruainen 1973) According to Finnish standards and the public health nurse s record on the family card they were un tidy and slovenly the mothers were tired and worn-out, and there were a great number of children per family The diet was unbalanced and unsatisfactory (Ha sunen and Pekkarinen 1971) The adults state of health was often not too good

At Nellim the economic standing was generally better even among the 1/1 Skolts, and gainful employment was easier to find Contacts with the world outside were also better

The Sasali village was an agricultural community on one of the major thorough fares in Lapland, with the result that contacts with the world outside were good but the people s lives were characterized by a sense of solidarity and a tendency to shut themselves off from outside influences. Many of the present parents had grown up in homes observing the »old-religious» customs, with a strict and serious view of life. Farming gave a relatively good yield, and a smooth rhythm of life was peculiar to the people The dwellings were often spacious, and the cleanliness was up to Finnish standards

The Tanhua population was dispersed over a wider area, and many homes had poor communications The village itself was served by a ferry but in the difficult road conditions of spring and autumn the village could only be reached by a long roundabout land route. The economic standing of the families showed great variation some families did well others suffered from unemployment and economic difficulties. Farming was underdeveloped and the chances of finding gainful employment other than in the forest and on road construction were small. There was strong motivation for the parents to send their children to school. Housing standards varied there were dwellings with modern conveniences but crowded cold and obsolete housing was frequent.

The attitude towards religion was usually completely indifferent.

Children s stay in a children s home

Ten 1/1 Skolt children (7 1 %) and two Finnish children (1 8) had lived in children s homes at ages under two years, usually because the mother had been ill. Two Skolt children had spent over a year in the children s home, the others, including the Finnish children 7—12 months.

School boarding-houses

Of the 1/1 Skolt children of Sevettijärvi and Nellim, 79 and 71 / respectively lived during the school term in boarding houses adjoining the school. Many of the Sevettijarvi children in particular could only visit their homes during the Christmas, Easter and summer holidays since the distance was so great Most of the 1/2 Skolts in Nellim lived close to villages

and only 26 % of the children stayed in the boarding house. No boarding house was provided for the Finnish children of Sassali since all lived sufficiently close to the school. Half of the Tanhua children, on the other hand, lived in the boarding house during school terms.

2. The parents' background

The parents' state of health

Eleven of the 34 1/1 Skolt mothers interviewed had either had a severe disease (lung tuberculosis, prolonged kidney disease) or were ill at the time of the examination (pronounced cardiovascular trouble, hypertension). Two of the 13 Skolt women married to Finns were ill. All the 27 Finnish mothers said they were in good health. In contrast to these healthy women, five of the 22 Finnish fathers interviewed were ill. One of the Finns of Nellim, married to a Skolt woman, was ill, against only two of the 29 Skolt fathers examined.

The parents' school-education

The parents' school-education is seen from Table 4. It should be noted that during the war years of 1939—44 the schooling was often irregular even for the Finnish children in the North, due to evacuation, teacher shortages, etc. However, the mean age of the fathers of the children in the 1/1 Skolt groups and the Finnish Sassali group was so high that most of them could normally have passed through the primary school before the outbreak of war. The same is true of the 1/1 Skolt mothers of Nellim. The differences between the educational standards of the groups is clearly visible, but it is also worth noting that the Tanhua group was in a much poorer position than the Sassali parents where more than half had completed a minimum of six years of primary school. Those with no schooling included two 1/1 Skolt mothers and one 1/1 Skolt father who were illiterate.

The parents' own upbringing

Many of the Skolt parents said that their own childhood had been hard and poor and they had had to start working early. Many had lost one of their parents in early childhood, and some had grown up in children's homes or with foster parents. Others said that they were given no food until work was done. A very common reply was: one had to obey, one glance from father was enough.

Table 5 shows the parents' opinion of their upbringing.

In 1967 the parents were not systematically asked about the upbringing in their childhood home. For three mothers (1/2 Skolts) there was a record of strict upbringing.

B. THE FAMILY AND THE PARENTS' ATTITUDE TO UPBRINGING

1. The parents and their attitude to child

Appraisal of the parents

During the discussion with the parents their general attitude to questions of upbringing, and their view of life on the whole, were appraised, both in respect of their intellectual and their emotional functions. Characteristics such as »narrow minded» »ordinary» and »broad minded» were used. The distribution of these characteristics is seen from Table 6.

Relationship between the married couple and atmosphere in the home

The impression obtained from the parents' indirect statements and their replies to direct questions was that the relationship between husband and wife on the whole was good and agreement prevailed on questions of upbringing. The largest number of divergent views was seen among the parents of Tanhua, where four of the 15 families were recorded as quarrelsome (26 %). In the Sassali group and the Nellim 1/1 and 1/2 Skolt groups only one family per group were recorded as quarrelsome, and in the Sevettijärvi group three of 26 (11.5 %).

TABLE 4

Parents' school education

School	Sevettijärvi + Nellim 1/1 Skolt		Nellim 1/2 Skolt		Sammall Finnish		Tanhua	
	F	M	F	M	F	M	F	M
No school	3	8	—	1	—	—	—	—
Ambulatory primary school or 1—2 years primary school	10	8	—	3	1	—	9	2
3—5	8	11	2	3	2	3	1	1
6—7	4	1	2	3	4	3	—	—
Complete primary school (8 years)	—	2	2	2	5	4	2	4
Lower secondary school (9 years)	—	—	—	—	—	—	—	1
Total	25	30	6	12	12	12	12	8

Ambulatory school = irregular teaching for few weeks to some months a year

TABLE 5

The parents' opinion of their upbringing

	Sevettijärvi 1/1 Skolt		Nellim 1/2 Skolt		Sammall Finnish		Tanhua	
	F	M	F	M	F	M	F	M
Strict	6	6	—	3	5	7	6	7
Mild	10	7	—	—	2	4	7	8

TABLE 6

Appraisal of the parents

	Sevettijärvi		Nellim 1/1 Skolt		Nellim 1/2 Skol		Sammall Finnish		Tanhua	
	M.	F	M	F	M.	F	M.	F	M.	F
»Narrow-minded»	6	5	3	2	3	0	2	2	1	2
»Ordinary»	16	15	5	4	7	1	9	6	9	7
»Broad-minded»	4	3	0	0	3	3	1	0	3	5
Total	26	23	8	6	13	4	12	8	15	14

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Wanted or unwanted children

In the discussion the parents were asked whether or not the child had been desired. When the contact was good this question was put directly otherwise the appraisal was made in connection with discussion about family planning In the event of families with more than six children, most parents said that they had not originally intended to have so many children but in spite of this no steps had been taken to limit the number of births Oral or other contraceptives were used in extremely few cases both among the Skolt Lapps and among the Finns. If the parents clearly expressed that they had not wanted so many children the actual child was annotated as »not desired if the parents comments were vague the child was reckoned as »not specially desired» In the cases of »desired child both parents declared that the child was wanted. In Sevettijärvi 46 Maternity Clinic cards carried information on the Skolt mother s reaction while expecting the child In the five cases where the mother s opinion now differed from the note made on the card the child was recorded among »not specially desired children» Table 7 shows that in about half the cases the children had been wanted apart from the Nellim 1/2 Skolt group in which 71 o of the children were said to have been wanted This group also showed the lowest number of directly unwelcome children, one out of 39

The Nellim 1/2 Skolt group contained the youngest parents and the lowest number of children per family The difference can therefore be explained by the fact that these families, usually with a relatively good economy still »had room» for more children The highest percentage of undesired children was found in the 1/1 Skolt families of Sevettijärvi and Nellim,

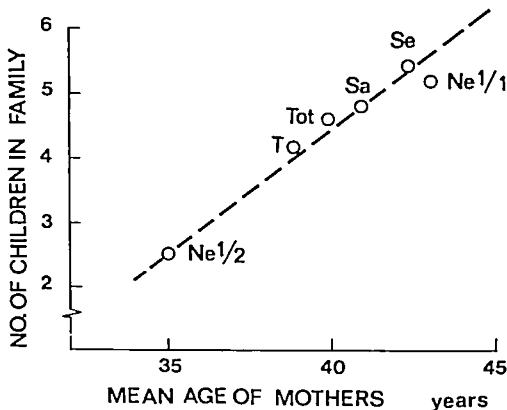


Fig 5. Size of family in relation t mothers ge.
Se = Sevettijarvi, N 1/1 = Nellim 1/1 Skolt,
Ne 1/2 = Nellim 1 2 Skolt, Sa = Sasall,
T = T nhua Tot = Total

TABLE 7

Parent attitude to child.

	Sevettijärvi 1/1 Skolt		Nellim 1/1 Skolt		Nellim 1/2 Skolt		Saamal Finnish		Tanhua Finnish		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Desired child	41	(45.1)	13	(54.2)	26	(71.8)	26	(59.1)	20	(52.6)	128	(54.2)
Not desired child	25	(27.5)	6	(25.0)	1	(2.6)	9	(20.5)	4	(10.5)	45	(19.1)
Not specially desired child	25	(27.5)	5	(20.8)	10	(25.6)	9	(20.5)	14	(36.8)	63	(26.7)
Total	91		24		39		44		38		236	

TABLE 8

Mother's attitude to her children

	Sevettijärvi + Nellim 1/1 Skolt		Nellim 1/2 Skolt		Saamali + Tanhua Finnish		Total	
	N	%	N	%	N	%	N	%
Warm	15	(44)	5	(39)	9	(33)	29	(39)
Neutral	15	(44)	6	(46)	11	(41)	32	(44)
Cool	4	(12)	2	(15)	3	(11)	9	(12)
Overprotective	0	(0)	0	(0)	4	(15)	4	(5)
Total	34		13		27		74	

χ^2 7.6 6 D F $p > 0.05$

TABLE 9

Father's attitude to his children

	Sevettijärvi Nellim 1/1 Skolt		Nellim 1/2 Skolt		Saamali Tanhua Finnish		Total	
	N	%	N	%	N	%	N	
Warm	16	(57)	4	(100)	13	(59)	33	(61)
Neutral	11	(39)	0	(0)	8	(36)	19	(35)
Cool	1	(4)	0	(0)	1	(5)	2	(4)
Overprotective	0	(0)	0	(0)	0	(0)	0	(0)
Total	28		4		22		54	

χ^2 2.82 D.F 4 $p > 0.1$

Wanted or unwanted children

In the discussion the parents were asked whether or not the child had been desired. When the contact was good this question was put directly, otherwise the appraisal was made in connection with discussion about family planning. In the event of families with more than six children most parents said that they had not originally intended to have so many children, but in spite of this no steps had been taken to limit the number of births. Oral or other contraceptives were used *in extremely few* cases both among the Skolt Lapps and among the Finns. If the parents clearly expressed that they had not wanted so many children the actual child was annotated as »not desired»; if the parents comments were vague the child was reckoned as »not specially desired». In the cases of »desired child» both parents declared that the child was wanted. In Sevettijärvi 46 Maternity Clinic cards carried information on the Skolt mother's reaction while expecting the child. In the five cases where the mother's opinion now differed from the note made on the card the child was recorded among »not specially desired children». Table 7 shows that in about half the cases the children had been wanted apart from the Nellim 1/2 Skolt group in which 71 of the children were said to have been wanted. This group also showed the lowest number of directly unwelcome children: one out of 39.

The Nellim 1/2 Skolt group contained the youngest parents and the lowest number of children per family. The difference can therefore be explained by the fact that these families, usually with a relatively good economy, still »had room» for more children. The highest percentage of undesired children was found in the 1/1 Skolt families of Sevettijärvi and Nellim,

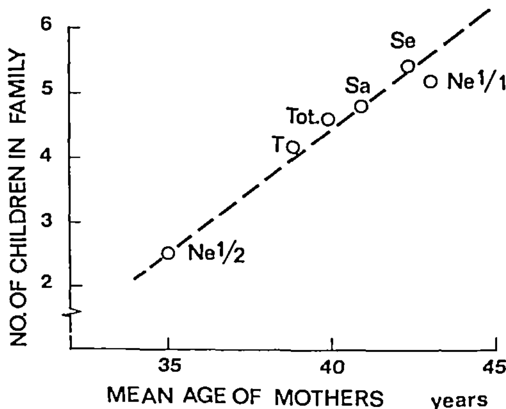


Fig 5. Size of family in relation to mothers age.
Se = Sevettijärvi, N 1/1 = Nellim 1/1 Skolt,
Ne 1/2 = Nellim 1/2 Skolt, Sa = Saariselkä,
T = Tanhua, Tot = Total

TABLE 10

Attachment to parents, Girls

	Sevettijärvi		Nellim 1/1 Skolt		Nellim 1/2 Skolt		Samall Finnish		Tanhua		Total	
	N		N	%	N	%	N	%	N		N	
T mother	14	(33.3)	8	(61.5)	2	(11 1)	9	(32.1)	4	(26.7)	37	(31.9)
T father	15	(35.7)	2	(15.4)	5	(27.8)	14	(50.0)	5	(33.3)	41	(35 3)
T both	13	(31.0)	3	(23.1)	11	(61 1)	5	(17 9)	6	(40 0)	38	(32.8)
Total	42		13		18		28		15		116	

χ^2 16.6. 8 D.F $p < 0.05$

TABLE 11

Attachment to parents, Boys

	Sevettijärvi		Nellim 1/1 Skolt		Nellim 1/2 Skol		Samall Finnish		Tanhua		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
T mother	13	(29 6)	4	(26.7)	3	(13.6)	3	(23.1)	8	(40.0)	31	(27.2)
T father	20	(45.4)	4	(26.7)	8	(36.4)	4	(30.8)	8	(40.0)	44	(38.6)
T both	11	(25.0)	7	(46.7)	11	(50 0)	6	(46.1)	4	(20.0)	39	(34.2)
Total	44		15		22		13		20		114	

χ^2 9.3 8 D.F $p > 0.05$

TABLE 12

Length of breast feeding period.

	Sevettijärvi		Nellim 1/1 Skolt		Nellim 1/2 Skolt		Samall Finnish		Tanhua		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Under 3 months	31	(28.7)	10	(32.2)	34	(77.3)	13	(26.5)	29	(50 0)	117	(40.3)
3—6	42	(38.8)	2	(6.4)	8	(18.2)	7	(14 3)	14	(24 1)	73	(25.2)
7—11	14	(12.9)	12	(38.7)	2	(4.5)	9	(18.4)	6	(10.3)	43	(14.8)
12—18	15	(13.8)	5	(16.1)	0	(0)	15	(30.6)	6	(10.3)	41	(14 1)
Over 18	5	(4.6)	2	(6.4)	0	(0)	4	(8.2)	3	(5.2)	14	(4.8)
Not known	1	(0.9)	0	(0)	0	(0)	1	(2.0)	0	(0)	2	(0.7)
Total	108		31		44		49		58		290	

the card recorded at the time of the event was given priority (Table 12)

No correlation was found between the length of the breast feeding period and the mother's age in any of the groups. For this reason the shorter breast feeding period among the 1/2 Skolt group of Nellim where the mothers mean age was lower must be considered a result of factors other than the low mean age

On the whole, the breast feeding period in the Skolt groups was shorter than that quoted by Mellbin (1962) for the Lapps, and also shorter than that recorded by Pelto (1962) during his study of 1958—59 Since that time, the public health nurses propaganda against a prolonged breast feeding period has gained ground In the village of Sassali, where the people were in general conservative about 40 % of the children were breast-fed for 12 months or more, a longer period than in any of the other groups

An explanation of the shorter breast feeding period among the 1/2 Skolts might be that the 1/2 Skolt mothers were in a better economic situation with better access to milk substitutes and information concerning them thanks to the shorter distance to the Child Health Centre It is also possible that the Nellim 1/2 Skolt mothers have been eager to accept the habits of the new culture into which they were married, with the result that the breast feeding periods became, from the pediatric point of view unsatisfactorily short.

Weaning

The mothers were asked separately for each child whether the weaning had been difficult, slightly difficult or easy In most cases, they found that weaning had been easy The most common reply was that the child no longer wanted the breast after bottle feeding had been begun or that the supply of breast milk had stopped The weaning was reported to have been easy by some 90 % of the Nellim 1/2 Skolt mothers and by 70—85 % of the mothers of the other groups.

Difficulties in weaning were reported by 10—11 % of the mothers in the groups other than the Nellim 1/2 Skolt mothers among whom only one out of 39 had found weaning to be difficult. This was a mother of 31 years whom the public health nurse requested to stop breast feeding when the child the youngest of her four children was 6 months old. This mother said »It was difficult for me, but the girl was easy to wean.»

In the other cases of difficult weaning the child was reported to have been restless and fretful for a long time and clung to the mother Methods such as spreading tar pepper or mustard onto the nipples, or »going away from home» out with the reindeer or on a fishing trip were very common among the Skolt mothers. A Finnish mother at Tanhua had said to her 2 year old daughter that there were worms in the milk.

The young mothers in the Nellim 1/2 Skolt group who began to bottle feed their children early had the least difficulties in weaning Otherwise the pattern was largely the same for the 1/1 Skolt and the Finnish mothers, and the methods of weaning were also the same as had been practised for generations.

4 Toilet training

When questions of cleanliness were discussed with the mothers their attitude to toilet training was graded as strict adequate or passive If the mothers said that they punished the child when an accident happened the toilet training was described as strict.

The Skolt mothers often spontaneously stressed that they did not start training until the child understood what it all was about

Table 13 reveals that five 1/1 Skolt mothers were recorded as permissive and nonchalant while none of the Finnish mothers at Sassali and only one each of the Tanhua mothers and the 1/2-Skolt mothers at Nellim, had been given this attribute. However the difference in attitude is not significant.

The mothers idea about the age at which their children were dry and clean appears from Table 13 a This suggests that the Finnish Sassali mothers and

TABLE 13

Mothers attitude to toilet training

	Sevettijärvi + Nellim 1/1 Skolt	Nellim 1/2 Skolt	Sanali	Tanhua	Total
			Finnish		
Attitude					
Strict	7	5	5	2	19
Adequate	20	7	7	12	46
Passiv	5	1	0	1	7
Total	32	13	12	15	72

χ^2 6.39 D.F 6 n. s.

TABLE 13

The mothers idea of the age at which their babies were clean and dry

	Sevettijärvi Nellim 1/1 Skolt	Nellim 1/2 Skolt	Sanali	Tanhua
			Finnish	
Under 1 1/2 years	6	7	10	3
1 1/2—2 years	17	3	1	6
Over 2 years	8	3	1	6
Total	31	13	12	15

the Skolt mothers married to Finns had a more active attitude towards toilet training — which proceeded according to the mothers wishes — than the Finnish mothers at Tanhua and the 1/1 Skolt mothers who were more permissive and were prepared to follow the child's own rhythm in toilet training This latter observation agrees with that reported by Pelto (1962)

5 Sex information

There were only a few individuals among the Finnish parents and the Skolt parents who reported that they had been told anything about matters of sex by their parents. Many mothers said they had been in complete ignorance at the time their first menstrual period began. For three Finnish mothers this had been the reason why they themselves gave their children full information about sex.

In the appraisal, when the parents said they had told the child that it grew inside the mother this was graded as »partial information If the child had also been informed of the father's role, this was graded as »complete information» The mothers gave detailed replies to these questions more often than the fathers, who often claimed that they did not know what the mother had told the children

The distribution of the information is shown in Table 14 which also shows that even if the difference is not significant for the whole group there is a significant tendency among the Finnish parents at Tanhua to inform their children. Although the Sanali parents on the whole had the best school education, it was difficult for these women who themselves had had a strict religious upbringing to speak of childbirth and the baby's origin with their own children.

TABLE 14

Sex information given by mother

	Sevettijärvi + Nellim 1/1 Skolt		Nellim 1/2 Skolt		Sasali Finnish		Tanhua		Total	
	N		N		N		N		N	%
Full information	2	(7)	1	(9)	1	(8)	5	(36)	9	(13)
Partial information	7	(23)	3	(27)	2	(17)	4	(29)	16	(24)
No information	21	(70)	7	(63)	9	(75)	5	(36)	42	(63)
Total	30		11		12		14		67	

$\chi^2 = 9.2$ 6 D.F. $p > 0.05$

Many of both the Finnish mothers and the Skolt women said they did not think it was wrong to give sex information to children but they could not possibly imagine giving such information themselves. Two Skolt fathers thought it was definitely wrong to tell children about sex, since they would then learn »things that are ugly and vulgar». The Finnish parents who had not given sex information to their children had usually told them that babies came from the hospital. One had spoken of the stork. One of the Skolt women had also told about the stork, two had said that babies were brought by a goose, one said it was a reindeer and one mother had said that spring babies come with the goose and autumn babies with Jack Frost. Most Skolt mothers, however, had said that babies were had from the cellar of the health station, from the public health nurse, or the like, which is understandable since a large number of deliveries take place in the health station.

The study shows that even among the Skolts, who for generations have lived closer to nature than the Finnish families, matters connected with sexual relationships and birth are considered shameful and should be concealed. However, illegitimate children are not uncommon among the Skolts. According to Lewin et al. (1971 a) 78 of the 625 births in 1925—64 (12.5 %) were illegitimate. The attitude to unmarried mothers was generally tolerant among the Lapps (Solem, Whitaker cited by Lewin et al. 1971 a). Only one mention concerned with sexuality has been found by the present author in the literature by Pälvänsalo (1953) who pointed out that among the Skolts a naked child was considered shameful. This would suggest that the development of the Skolts' present opinion has not been influenced by their contacts with Finnish culture. However, it is difficult to draw any conclusions on the basis of the present material.

6. *Corporal punishment*

Both parents were asked about corporal punishment. The replies were graded according to a scale of three grades: no corporal punishment, mild corporal punishment, and a real spanking. Table 15 reports the more severe degree, that is to say, if only one of the parents had used spanking as a punishment it was entered as a case of spanking.

It is striking that the mothers of the 1/2 Skolt group of Nellim were more strict in their upbringing than those of the other groups (none of the four interviewed fathers of the 1/2 Skolt group practised corporal punishment). This can be interpreted to mean that the 1/2 Skolt mothers, under the pressure of two different cultures, go too far in their efforts to »make a success of» with their children and use more severe methods than either the Finnish mothers or the Skolt mothers who have married within their own culture.

TABLE 15

Use of corporal punishment

	Sevettijärvi + Nellim 1/1 Skolt		Nellim 1/2 Skolt		Sassali + Tanhua Finnish		Total	
	N	%	N	%	N	%	N	%
Severe use	2	(6)	5	(39)	2	(7)	9	(12)
Slight use	21	(60)	3	(23)	12	(44)	36	(48)
No use	12	(34)	5	(39)	13	(48)	30	(40)
Total	35		13		27		75	

χ^2 12.8 4 D.F $p < 0.02$

TABLE 16

Mother's condition during pregnancy

	Sevettijärvi 1/1 Skolt		Nellim 1/1 Skolt		Nellim 1/2 Skolt		Sassali Finnish		Tanhua Finnish		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Good	80	(71.4)	26	(92.9)	39	(88.4)	42	(84.0)	46	(79.3)	233	(79.8)
Not good	32	(28.6)	2	(7.1)	5	(11.6)	8	(16.0)	12	(20.7)	59	(20.2)
Total	112		28		44		50		58		292	

In all groups, the percentage of parents who never made use of corporal punishment in their upbringing was approximately the same.

The result disproves the opinion which has been advanced in the older literature that the Skolt Lapps never use corporal punishment in bringing up their children. Almost half the parents reported that their own upbringing had been strict (p. 32). According to Pelto (1962) also, corporal punishment occurred among the Skolts.

C. PHYSICAL HEALTH AND DEVELOPMENT

1 *Pregnancy, delivery, birth-weight*

The mother's condition during pregnancy

The mothers were questioned about their health during each pregnancy and the information they gave was compared with that on the Maternity Clinic and Child Health Centre cards.

Table 16 shows the distribution of mothers with and without ill-health during pregnancy by groups. Ill health covers nausea, hypertension, albuminuria, oedema, and severe fatigue.

The highest rate of disturbances was noted for Sevettijärvi and Tanhua, the two most isolated places and the furthest away from medical help.

Delivery

The frequency of deviations from normal delivery was highest among the 1/2 Skolts of Nellim (20 %) where induced labour and Caesarean section were the most common deviations, 7 % each. The rate of complications among the Sevettijärvi mothers and the Finnish mothers was the same, about 11 % whereas the 1/1 Skolt

TABLE 17

Place of delivery

	Sevettijärvi		Nellim 1/1 Skolt		Nellim 1/2 Skolt		Sammali		Tanhua Finnish		Total	
	N		N		N		N	%	N	%	N	
At home without help	32	(28.6)	3	(9.7)	1	(2.8)	0	(0)	0	(0)	36	(12.9)
At home with professional help	14	(12.5)	14	(12.9)	0	(0)	11	(22.9)	6	(11.5)	35	(12.5)
In local health house	38	(33.9)	0	(0)	0	(0)	0	(0)	0	(0)	38	(13.6)
In hospital	27	(24.1)	22	(71.0)	35	(97.2)	37	(77.1)	46	(88.5)	16	(59.9)
Elsewhere	1	(0.9)	2	(6.5)	0	(0)	0	(0)	0	(0)	3	(1.1)
Total	112		31		36		48		52		279	

TABLE 18

Mean birth weights in different groups (multiple births not included)

	Sevettijärvi + Nellim 1/1 Skolt	Nellim 1/2 Skolt	Sammali + Tanhua Finnish
Boys	N 60	N 20	N 40
Mean birth-weight in g	3317	3414	3356
S. D	557	422	635
Girls	N 56	N 20	N 59
Mean birth-weight in g	3203	3187	3600
S. D	505	606	498

1/1 Skolt boys/Finnish boys t value = 1.67 $p > 0.1$
1/1 Skolt girls/Finnish girls t value = 4.13 $p < 0.01$

TABLE 19

State of physical health

	Sevettijärvi		Nellim 1/1 Skolt		Nellim 1/2 Skolt		Sammali + Tanhua Finnish		Total	
	N	%	N	%	N		N		N	%
No disease	55	(48.7)	23	(74.1)	33	(75.0)	81	(73.6)	192	(64.4)
Infections	18	(15.9)	2	(6.4)	1	(2.3)	12	(10.9)	33	(11.1)
Accidents	5	(4.4)	0	(0)	0	(0)	3	(2.7)	8	(2.7)
Other disorders	35	(30.9)	6	(19.4)	10	(22.7)	14	(12.7)	65	(21.8)
Total	113		31		44		110		298	

If the groups with somatic disorders are combined the chi square test gives the result $p < 0.001$ (χ^2 19.7 3 D F)

mothers of Nellim had a rate of only about 4 %. It is worth mentioning that the 108 deliveries of the Finnish mothers included six mothers with a breech presentation, whereas no breech presentation was reported among the 184 deliveries of 1/1 and 1/2 Skolts.

Table 17 shows that almost half of all deliveries among the Sevettijärvi Skolts took place at home and in 32 cases (28 %) there was no professional help. All the Finnish mothers had had professional help (public health nurse or midwife) even though 17 % of the deliveries took place at home. Among the 1/2 Skolts of Nellim, all but one of the deliveries took place in hospital.

It is therefore natural that the highest rate of medical interference and procedures should have been among the 1/2 Skolt mothers since the majority resorted to hospital services for their deliveries.

Birth weight of the child

The children's birth weights in the different groups are seen from Table 18.

The fact that the Finnish girls in the present material have a slightly higher birth-weight than the boys cannot be explained. According to Tiisala and Kantero (1971) the mean birth-weight of Finnish boys is 3.66 ± 0.51 kg and that of Finnish girls 3.42 ± 0.4 kg. According to Hultin (1973) the means are 3.58 kg for boys and 3.42 kg for girls.

2. *Physical health*

At the present examinations, the children of all groups were in good health as regards acute illness but especially in Sevettijärvi there were children in poor general condition with a poor nutritional status. Some younger children who were extremely pot bellied were included in Table 19 under the heading »other disorders».

The incidence of somatic illness was noted down according to the mothers' reports and checked from the Child Health Centre cards and school health cards. Sporadic data on minor infections were not entered, but if a child had had ear infection or respiratory tract infection on not less than three occasions, a predisposition to infections was noted down.

The results can be seen from Table 19 in which the two Finnish groups are combined since they showed very good agreement.

The rate of ear infections, especially was high in Sevettijärvi. Despite the exceedingly high infection rate, the erythrocyte sedimentation rate was not higher than for the other groups. The mean ESR for all groups but one was about 7—8 mm/h. The Finnish children of the Tanhua group had a mean ESR of 11.7 mm/h.

No case of albuminuria or glucosuria was traced by means of Albustix or Clinistix either in the Skolt groups or among the Finnish children.

The dental status can be considered to reflect the state of health and the individual health care to a certain extent. For this reason a review of the dental status in the present material is given in Table 20. The Skolt groups were examined by a dentist*) whereas the control group was examined by the pediatrician, according to the same principles of evaluation. The dental status of the Skolt groups was approximately the same throughout. The fact pointed out by Hasunen and Pekkarinen (1971) viz. that the diet of the Sevettijärvi Skolts contained more sugar and white bread and considerably less milk than that of the other Skolt groups was not borne out by their dental status. The Sassali group differed markedly from all the other groups in that only one of the 48 children had bad teeth.

4. *Growth*

The anthropometric measurements were carried out on the Skolts in the course of their expeditions by Lewin (1971 c) and his co-workers who also made the statistical analyses.

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*) Dental status was examined at Sevettijärvi and Nellim by P. Kirveskari, Lic. Odont.

TABLE 20

Dental status

	Sevettijärvi		Nellim 1/1 Skolt		Nellim 1/2 Skolt		Sammalli Finnish		T nbua		Total	
	N		N		N		N		N		N	%
Good	34	(37.0)	8	(25.8)	10	(23.3)	48	(96.0)	14	(38.9)	114	(45.2)
Moderate	41	(44.6)	17	(54.8)	26	(60.5)	0	(0)	8	(22.2)	92	(36.5)
Bad	16	(17.4)	6	(19.4)	7	(16.3)	1	(2.0)	14	(38.9)	44	(17.5)
Children < 1 year	1	(1.1)	0	(0)	0	(0)	1	(2.0)	0	(0)	2	(0.8)
Total	92		31		43		50		36		252	

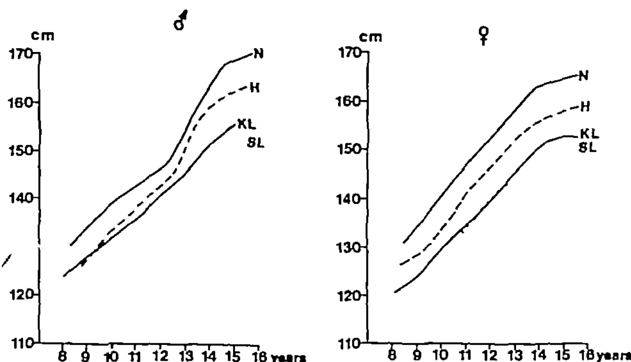


Fig. 6. Growth diagrams for Skolt Lapp children (SL) children of Kautokeino Lapps (KL) and North Norwegian children of Norwegian fathers and Kautokeino Lapp mothers (H) and for genuine Norwegian children in North Norway (N). The diagram shows how the growth follows the socio-economic conditions, which are best for the group of genuine Norwegian children and poorest for the Sevettijärvi Skolt children. The poor socio-economic conditions in Sevettijärvi affects the growth of the boys more than that of the girls. Diagrams by Lewin et al. (1971)

The Skolt children of Sevettijärvi are already in the first years of life of a shorter stature than the Finnish children. Their height at these ages is 3—4 below that of the Finnish children and at the ages of 14—15 years about 8—9

The Sevettijärvi Skolt boys were considerably smaller both in weight and height than the other Lapp groups. When the Skolt girls are compared with other Lapp groups, the same finding is made. Their weight, however shows an even

greater difference, relatively than their height. Fig 6

The Nellim Skolts show for the boys, heights that exceed the average for the Sevettijärvi Skolts. The Nellim girls also are distinctly ahead of the Sevettijärvi girls. The difference is even more pronounced between the 1/2 Skolts of Nellim and the Sevettijärvi Skolts. The 1/2 Skolt children are approximately at the same level above the Sevettijärvi Skolts as the Finnish children as regards height and weight. The differences in growth are evidently partly a manifestation of the different socio-economic standards. The Nellim 1/2 Skolts have better socio-economic conditions than the 1/1 Skolts and especially in Sevettijärvi the nutritional conditions are the poorest. This growth pattern confirms the finding that boys are more sensitive than girls to growth retarding factors (Greulich 1951 *Graffar and Corbier 1966*)

In the last ten years the Sevettijärvi Skolts have largely caught up with the Nellim Skolts both in height and weight, despite conditions of continued isolation. This can be attributed to their improved standard of living In spite of this the children in Sevettijärvi today follow the same growth patterns as the children of nomadic Lapps in Sweden 15—20 years ago (Lewin et al 1971 c)

4 Psychomotor development

Psychomotor development was evaluated on the basis of entries on the child health centre cards made when the child was seen for follow up examinations by the public health nurse or the physician, and on the basis of their mothers statements. In the event of a discrepancy the health card entry was considered valid.

The age at which the child first sat

The Nellim 1/2 Skolt children were, as a rule, said to have learnt to sit slightly earlier than the children of the other groups. Compared with the Sevettijärvi Skolts and the Finnish groups, the difference was over a month (Table 21)

The age at which the child began to walk

In learning to walk, the 1/2 Skolt group of Nellim showed relatively late development. About 80 % of these children had learnt to walk before the age of 14 months, against 98 % of the Finnish children of Tanhua and 91 / of the Skolt children of Sevettijärvi. On the other hand, both of these groups included one child who *had not learnt to walk until after the age* of two years.

The age at which the child began to speak

The age at which the first words were spoken was also much the same for the different groups. 72—79 % of the children were reported to have uttered their first words before 14 months of age, except the Finnish children of Sassali for whom *the percentage was only* 45.5 / *Of the* Sassali children, 23 % were reported to have said their first words after the age of 18 months, a percentage higher than for any other group It is difficult to find an explanation for this phenomenon, but the figures seem to prove in any case that the bilingualism in Skolt families did not affect the speech development of the

TABLE 21

Mean age of sitting

	Sevettijärvi	Nellim	Nellim	Sassali	Tanhua	Total
	1/1 Skolt		1/2 Skolt	Finnish		
Number	62	22	26	43	30	183
Mean (months)	7 4	7.0	6.2	7 6	7 4	7.2
S. D	1.8	1.0	1 0	1.5	1.3	1.5

TABLE 22

Results of the Oseretsky test of motor proficiency

	I Sevettijärvi 1/1 Skolts girls N 23		II boys N 27		III Finnish girls N 24		IV boys N 23	
Means of MQ with SD	112.5	15.6	96.2	10.3	107.3	16.8	106.6	14.3
T-test performed between	I and II t-value	p	I and III t-value	p	II and IV t-value	p	III and IV t-value	p
	4.44	< 0.001	1.11	n.s.	3.0	< 0.01	0.14	n.s.

TABLE 23

MQ means according to cooperation

	Sevettijärvi			Finnish				
Boys	N	MQ	S. D	N	MQ	S. D.	t-test	p
Cooperating + neutral	20	97.0	11.6	20	106.9	14.3	2.39	< 0.05
Negative	7	93.9	4.0	3	104.7	16.7		
Girls								
Cooperating + neutral	19	115.1	15.2	23	108.0	16.7	1.42	> 0.1
Negative	4	100.3	11.6	1	90.0	0		

TABLE 24

Distribution of MQ with Oseretsky test of motor proficiency

MQ	Sevettijärvi 1/1 Skolt boys	1/1 Skolt girls	Finnish Boys	Girls
80—89	8	5	3	3
90—109	15	12	9	12
110—129	4	4	9	6
Over 130	—	2	2	3
Total	27	23	23	24

Skolt children in late infancy

Oseretsky's test for motor proficiency

The test was carried out on primary school children in their 2nd to 6th year of school. The results can be seen from Table 22.

The Sevettijärvi boys had significantly poorer motor performances than the Finnish boys and the Sevettijärvi girls. No differences could be shown between the Finnish girls and the Sevettijärvi girls, any more than between the Finnish girls and Finnish boys.

The problem is whether the Sevettijärvi boys are really less good or whether they are less cooperative. The differences in cooperation can be seen from Table 44

TABLE 25

IQ means in schoolchildren (WISC)

	Sevettijärvi				Finnish			
	I		II		III		IV	
	1/1 Skolt							
	girls N 40		boys N 44		girls N 34		boys N 34	
		SD		SD		SD		SD
IQ Full Scale	97 42	14.2	91.04	14.8	97.29	12.9	101.56	12.4
IQ Verbal Scale	96.22	13.5	92.63	16.1	98.73	14.9	104.12	12.1
IQ Performance S.	99 05	15.3	90.45	14 7	96.51	10.9	98.26	14.2
					) N 35			

T-test performed between	I and II		I and III		II and IV		III and IV	
	t-value	p	t-value	p	t-value	p	-value	p
Full Scale	2.01	< 0.05	0.76	n.s.	3.33	< 0.01	1.39	n.s.
Verbal Scale	1 10	n.s.	0.76	n.s.	3.46	< 0.02	1.64	n.s.
Performance Scale	2.62	< 0.02	0.82	n.s.	2.96	< 0.03	0.57	n.s.

) One girl was inhibited to such degree that she refused to do the verbal scale.

The results in Oseretsky s test when the not cooperating children are excluded is shown in Table 23

In no case was the MQ under 80 The distribution of MQ can be seen from Table 24

For none of the boys did the result exceed 140 which it did for two Finnish and two Skolt girls. None of the Skolt boys exceeded 120 which in all the other groups was exceeded by some children

The Sevettijärvi Skolt boys, therefore, were distinctly poorer in their motor performances than the children of the other groups.

No correlation between the results of Bender s, Goodenough s and Oseretsky's tests could be shown, nor could any correlation be shown between birth complications and Oseretsky's test.

D INTELLECTUAL FUNCTIONS

Intelligence studies

The Wechsler Intelligence Scale for Children (WISC) tested on school-aged children, gave the results shown in Table 25

A comparison of the mean values by means of the t test showed that the Sevettijärvi Skolt boys were significantly poorer in their achievements in both the Verbal and the Performance Scale of Wechsler test than the Finnish boys.

Similarly there was a significant difference between the Full Scale means of the Sevettijärvi Skolt boys and the Finnish boys. The Sevettijärvi Skolt boys had also a significantly poorer result in the Full Scale and the Performance part than the Sevettijärvi Skolt girls. In the Verbal Scale there was no significant difference between Skolt boys and girls.

No significant difference was found between the Finnish boys and the Finnish girls.

To test whether the poorer results of the Skolt boys could be attributed to their unwillingness to cooperate the children were distributed into groups according to their cooperating ability The results obtained are shown in Table 26 A significant difference is seen in the means for Full Scale-test and in the verbal capacity but not in the Performance Scale. However these differences between the cooperating and the negative groups were not significant. This indi-

TABLE 22

Results of the Oseretsky test of motor proficiency

	Sevettijärvi 1/1 Skolts				Finnish			
	I girls N 23		II boys N 27		III girls N 24		IV boys N 23	
Means of MQ with SD	112.5	15.6	96.2	10.5	107.5	16.8	106.6	14.5
T-test performed between	I and II		I and III		II and IV		III and IV	
	t-value	p	t-value	p	t-value	p	t-value	p
	4 44	< 0.001	1 11	n.s.	3.0	< 0.01	0.14	n.s.

TABLE 23

MQ means according to cooperation

	Sevettijärvi			Finnish				
Boys	N	MQ	S. D	N	MQ	S. D	t-test	p
Cooperating + neutral	20	97 0	11 6	20	106.9	14.5	2.59	< 0.05
Negative	7	93.9	4 0	3	101 7	16.7		
Girls								
Cooperating + neutral	19	115.1	15.2	23	108.0	16.7	1 42	> 0.1
Negative	4	100.5	11 6	1	90.0	0		

TABLE 24

Distribution of MQ with Oseretsky test of motor proficiency

	Sevettijärvi		Finnish	
MQ	1/1 Skolt boys	1/1 Skolt girls	Boys	Girls
80— 89	8	5	3	3
90—109	15	12	9	12
110—129	4	4	9	6
Over 130	—	2	2	3
Total	27	23	23	24

Skolt children in late infancy

Oseretsky s test for motor proficiency

The test was carried out on primary school children in their 2nd to 6th year of school The results can be seen from Table 22

The Sevettijärvi boys had significantly poorer motor performances than the Finnish boys and the Sevettijärvi girls. No differences could be shown between the Finnish girls and the Sevettijärvi girls, any more than between the Finnish girls and Finnish boys.

The problem is whether the Sevettijärvi boys are really less good or whether they are less cooperative. The differences in cooperation can be seen from Table 44

TABLE 27

Distribution of IQ (WISC, F S.) ages 7—15 years

	Sevettijärvi girls	1/1 Skolt boys	Finnish girls	boys
IQ				
Below 60	0	1	0	0
60— 69	2	1	0	0
70— 79	2	4	4	2
80— 89	5	11	5	4
90— 99	14	16	10	10
100—109	10	6	5	6
110—119	5	4	10	11
120—129	1	1	0	1
Over 130	1	0	0	0
Total	40	44	34	34

TABLE 28

Means of Stencil Design, Kohs-Häkkinen Cube tests and Bender test

	Sevettijärvi 1/1 Skolt				Finnish			
	I girls N 39	SD	II boys N 43	SD	III girls N 33	SD	IV boys N 34	SD
Kohs-Häkkinen	107.6	15.3	100.8	14.5	97.4	9.9	101.8	17.8
Stencil Design	105.1	15.1	101.7	15.1	97.2	13.7	104.6	15.2
Bender	62.3	45.6	62.3	37.2	53.3	34.3	50.5	29.5
T-tests performed between	I and II		I and III		II and IV		III and IV	
	t-value	p	t-value	p	t-value	p	t-value	p
Kohs-Häkkinen	2	< 0.05	3.2	< 0.01	0.37	n.s.	1.3	n.s.
Stencil Design	1.02	n.s.	2.33	< 0.05	0.83	n.s.	2.11	< 0.05
Bender	0.01	n.s.	0.97	n.s.	1.51	n.s.	0.35	n.s.

järvi girls between the results in Full Scale and Verbal Scale which shows that cooperation to some degree influences the achievement (Table 26 a).

An analysis of the different components in the test scale discloses that the Sevettijärvi Skolt children had poorer results throughout than the Finnish children in all tasks other than Picture Completion test. In this test the faculty of observation is important, and it may be assumed that the Skolt children whose upbringing is largely based on imitation and who are used to observing contours and shapes when they move about in the forest, have practised this faculty ever since their early childhood (Kava 1971 Seitamo 1972).

The distribution of IQ is shown in Table 27

The preschool-age children in Sevettijärvi did the TML-test. One Skolt boy had IQ 54 All the others results were over 80 (21 children) Only three Finnish preschool-age children did the TML, and 29 the KTK test. One girl had in KTK test a result of 79 all the other children above 86

Thus two of the Sevettijärvi-children must be classified as imbecile[1]) Two girls and one boy had an IQ between 60—69 (WISC)[2]) Three boys[3]) had IQs of 71 74 and 75 respectively

None of the children of the Nellim 1/1 and 1/2 Skolt groups had an IQ under 80

One of the children of the examined Finnish families a boy of nine, was in an establishment for mentally retarded Diagnosis Autismus infantilis. Imbecillitas (Not examined by the pediatric team)

Otherwise there was no IQ under 70 among the Finnish children. One girl had an IQ of 72[4]) another girl and two boys had IQs of 75[5])

1) Examined t the Department of Pediatrics of the University of Oulu. Case 111 boy of 8, born prematurely birthweight 2000 g and signs of organic brai damage. WISC F S 40 P S. 50, V S. 48. Case 405 boy aged 2 years 9 months, b.w 3460 g Signs of brain damage, with tactic gait. Autistic traits. IQ TML 54

2) Case 212 girl aged 7 years 10 months, signs of organic brain damage (WISC F S. 66 P S. 60 V S. 72) Examined at the Department of Pediatrics. Case 73 girl aged 6 years 8 months, one of set of triplets, C hild, b. w 2330 g (IQ F S. 61 P S. 75 V S. 55) KTK 94 and Goodenough 72. Evident verbal weakness.

Case 70 one yea older brother to case 73 bove IQ F S. 62, P S. 72, V S. 60 KTK 88, Goodenough 84 i. e. verbal weakness.

3) Brothers t cases 73 nd 70 bove

Case 71 Triplet A, b. w 2960 g IQ F S. 71 P S. 62, V S. 66, KTK 101 Goodenough 86.

Case 72 Triplet B, b. w 2260 g, IQ F S. 74 P S. 92, V S. 62, KTK 96, Goodenough 91

Case 9 n elder brother t these siblings, 12 years 6 months. IQ F S. 75 P S. 75 V S. 79 KTK 79 Goodenough 94 H later moved t an auxiliary school.

There are nine children the family of these siblings. The parents were described as warm with positive ttitud their children, and ordinary in their views of life. The mother was not fully proficient in Finnish, but did not seem to be feeble minded. However poor verbal achievement is pronounced in all the described children, the eldest boy (no 9) mastered the language best. F milial feeble-mindedness was pparently not involved, since the non-verbal tasks were usually better sometimes almost normal.

4) Case no 1067: girl ged 7 years 9 months. She had had convulsions in infancy nd preschool age No particular neurological findings. WISC F S. 72 P S. 73 V S. 73 KTK 96, Goodenough 84 She went t normal school but had failed t pass beyond Form I

5) Case 1092: Gi l ged 7 years 3 months. IQ WISC F S. 75, P S. 83, V S. 72, KTK 96, Goodenough 81 Verbal bility poor The fourth of 7 siblings. An elder sister had impaired hearing due to otitis. 18-month old twins t home Farmer' home with much work, parents had little time for children. Case no 1050 boy ged 12. WISC F S. 75, P S. 75 V S. 79, KTK 80 Goodenough 89 B. w 2600 g The mother had suffered from severe nausea during pregnancy The boy had had convulsions i infancy No obvious signs of brai damage.

Case 1022 boy ged 14 years with reduced eyesight and nystagmus. Otherwise no particular neurologic findings. IQ 75, TML. H had been t the auxiliary school but had to lea since he could not get along with the manageress of the boarding school.

Five of the 1/1 Skolt children (3 4 %) thus fall below the limit of mental subnormality One of the 110 Finnish children belonged to this category If all the children with IQ 75 or less are included, the figures are 8 (5.5 %) for the 1/1 Skolts and 5 (4.5 %) for the Finnish children It should also be borne in mind that the Sevettijärvi material contains a set of triplets and two children with pronounced verbal weakness Broadly speaking the frequency of mental subnormality is of the same order in both groups and considerably exceeds that reported by Amnell (1964) and Kaila (1942) However, since the population groups are small no comparisons can be made

KTK test

The children were examined with two subtests of the KTK Scale the Stencil Design and Kohs-Häkkinen test

The results for the school-aged are shown in Table 28 It can be seen that the Sevettijärvi girls are significantly better than the Finnish girls and the Sevettijärvi boys. The difference between the Finnish boys and the Sevettijärvi boys was

not significant which is remarkable since the Skolt boys in most other tests had produced poorer results, partly because of a lack of motivation to do well. This can be interpreted to mean that the test measures a component (observation, visuomotor faculty) which is well developed in the Skolts.

Bender's Visuomotor Gestalt test

The results of the Bender test on school children are presented in Table 28 No statistically significant differences were obtained in the overall result. According to Kava (1971), the children of the two groups made mistakes of different kinds the Sevettijärvi children made fewer changes and placed the figures more freely on the paper than the Finnish children.

The difference concerning the change was statistically significant. This apparently reflects the greater adherence of the Finnish children to rules and norms and their greater ambition for precision.

Goodenough's Draw-a man test

No differences in IQ calculated on the basis of Goodenough's test could be shown between the groups (Table 28 a)

TABLE 28 a.

IQ on the basis of Goodenough Draw-a-man test

	Sevettijärvi 1/1 Skol	Finnish
N	81	68
IQ	98 6	99 6
S D	14 6	14.8

-value = 0.41 p = n. s.

There were no statistically demonstrable differences between the component factors, either, apart from height, the Sevettijärvi children drawing statistically significantly taller human shapes than the Finnish children (Kava) The Skolt Lapps are the shortest known European population, the mean height of men is 161 cm and of women 146 9 cm, even though the mean height of the Skolt children is steadily increasing (T Lewin 1971 c) According to Dennis (cited by Kava 1971), the children of a culture that is being assimilated draw an idealized man, instead of drawing the type of people they see most often.

School performance

A high percentage of the Skolt school children between the ages of 7—10 years, 20 % of the whole group studied and followed up failed to move up to a higher form every year The performances improve slightly in the later years partly because the children's verbal capacity improves However motivation for advanced school education is infrequent, and there are numerous drop-outs from school. Only 24 % of the Skolt boys in Sevettijärvi liked school, against 65 % among the Finnish boys. The percentages for girls were 58 and 87 respectively (Sertamo 1972)

E. PSYCHOSOMATIC AND NERVOUS SYMPTOMS

1 Sleeping habits and sleeping disturbances

Owing to the great variation in the hours of daylight and darkness at the different seasons of the year in these latitudes the people's sleeping habits also vary according to the daylight conditions. Bedtime for children below school age and for those in the first few years of school was reported to be about 19 o clock among the Finns and 19—20 among the Skolts. During the summer with long hours of daylight, the Skolts said their children went to bed any time between 20 and 23 o clock. However when we were out in the village about midnight, small children were still playing outdoors. Replies to the effect that they can go to bed when they feel tired» were also recorded The Finns were somewhat stricter about bedtime, even in the summer When visiting the Skolt homes during the summer half of the year both big and little children could be found still sound asleep about noon

Concerning bedtime rituals, most Skolt mothers said that the children made the

sign of the cross (an Orthodox habit) before they went to sleep and many school age children said their evening prayers which they had learnt at school. Both the Skolt and the Finnish mothers said that they seldom had time to rock or lull their children to sleep to tell a bed time story or the like For the elder child ren in a large family this had sometimes been done perhaps by a maternal or paternal grandmother

During the interview the mothers were questioned about their children s sleep difficulties of going to sleep, waking at night nightmares and somnambulism From the age of 7 upwards sleep was discussed with the children themselves

If one of the above phenomena occur red once or twice a week, the sleeping disturbances were described as moderate but if they occurred more often they were described as severe

Only children over 4 years of age were included in the statistical calculation since it is difficult to evaluate the sleeping disturbances of small children. Such an evaluation would have required a more detailed analysis than was possible in connection with the present study It is also true of the older children s sleeping disturbances that the grading at the same time measures the parents sensitivity and faculty of observation The mother s own sleep plays a part if she is a light sleeper she registers more disturbances than a mother with a sounder sleep

Sleeping disturbances were distributed over the various groups as shown in Table 29 The differences between the groups were not statistically significant The fre quencies on the whole, are somewhat higher than the 14 % reported by Jonsson and Kälvesten (1964), but the criteria have apparently been different

2 *Headache*

Mothers of children aged over 7 years, and the children themselves were inquir ed about headache If refractive eye defects had been recorded the replies were not entered nor were replies such as »in connection with temperature rise» Replies indicating headache once a week or more were entered as frequent the others as occasional (1—2 times a month)

The results are shown in Table 30, according to which there was no signifi cant difference between the groups.

20 6 % of the material examined had headaches the frequency level is much the same as shown by Jonsson and Kälves ten (1961) for Stockholm boys aged 7—15 years (17) and \ Harnack (1953) among children aged 10—11 years

3 *Poor appetite*

The kind of appetite as described by the parents or the children themselves, can be seen from Table 31

The results agree with the earlier opi nions according to which fussiness about

TABLE 29

Sleeping disturbances in children over 4 years of age

	Sevettijärvi		Nellim 1/1 Skolt		Nellim 1/2 Skolt		Sammalt + T ahua Γ nkh		Total	
	N	%	N	%	N		N		N	%
Good sleep	77	(81 0)	27	(90.0)	32	(88.9)	67	(74 4)	202	(80.8)
Moderate disturbances	15	(15.8)	2	(6.6)	4	(11 1)	22	(24 4)	43	(17.2)
Severe	3	(3.1)	1	(3.3)	0	(0)	1	(1 1)	5	(2.0)
Total	95		30		36		90		250	

χ^2 8.6 6 D.F p > 0 1

TABLE 30

Headache in children over 7 years of age

	Sevettijärvi 1/1 Skolt		Nellim 1/1 Skolt		Nellim 1/2 Skolt		Sammali + Tanhua Finnish		Total	
	N	%	N	%	N	%	N	%	N	%
No headache	63	(82.9)	17	(65.4)	20	(83.3)	54	(79.4)	154	(79.4)
Occasionally	10	(13.1)	6	(23.1)	3	(12.5)	12	(17.7)	31	(16.0)
Often	3	(3.9)	3	(11.5)	1	(4.2)	2	(2.9)	9	(4.6)
Total	76		26		24		68		194	

χ^2 3.5 6 D.F $p > 0.1$

TABLE 31

Anorexia in children over 4 years of age

Appetite	Sevettijärvi 1/1 Skolt		Nellim 1/1 Skolt		Nellim 1/2 Skolt		Sammali Finnish		Tanhua Finnish		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Good	80	(86.0)	24	(80.0)	21	(58.3)	20	(52.6)	32	(62.8)	117	(71.3)
Not very good	9	(9.7)	0	(0)	7	(19.4)	9	(23.7)	12	(23.5)	37	(14.9)
Poor	4	(4.3)	6	(20.0)	8	(22.2)	9	(23.7)	7	(13.7)	34	(13.8)
Total	93		30		36		38		51		248	

χ^2 29.1 8 D.F $P < 0.001$

food is a problem of civilisation (Brenneman 1932, v. Harnack 1953, Annell 1959).

The percentage of children with a poor appetite increases in the groups with better economic standing and is lowest among the Sevettijärvi children who sometimes may not even have enough to eat. When asked if the children refused to eat, a Sevettijärvi Skolt mother answered: »In our circumstances there is no point in being fussy about food. We are lucky if we always have something to put on the table.» The difference between Sevettijärvi and Sammali is greater than between Sevettijärvi and Tanhua, where there were also homes with economic difficulties.

4. Abdominal pain

In children over 4 years of age, the occurrence, once or twice a month, of abdominal pain without a rise in temperature and with no vomiting, was entered as »occasional», once a week or more as »often». The mothers and also the children over 7 years of age were questioned. Even those cases in which only the child reported abdominal pain were included in the table (Table 32), which shows the frequencies and their distribution.

No significant difference was observed between the groups, nor was there any demonstrable difference between the Finnish groups. It is naturally not certain that all the included cases of recurrent abdominal pain were of psychogenic

TABLE 32

Abdominal pain. Children over 4 years of age

	Sevettijärvi		Nellim 1/1 Skolt		Nellim 1/2 Skolt		Sanali + Tanhua Finnish		Total	
	N	%	N	%	N	%	N	%	N	%
No pain	78	(82.1)	24	(80.0)	24	(66.7)	65	(70.6)	191	(75.4)
Occasional	16	(16.8)	6	(20.0)	8	(22.2)	18	(19.5)	48	(19.1)
Frequent	1	(1.1)	0	(0)	4	(11.1)	9	(9.7)	14	(5.5)
Total	95		30		36		92		253	

χ^2 11.9 6 D.F. $p > 0.05$

TABLE 33

Abdominal pain. Children over 7 years of age

	Sevettijärvi 1/1 Skolt	Sanali + Tanhua Finnish	Total
	N	N	N
No pain	61	45	106
Occasional pain	14	16	30
Frequent pain	1	7	8
Total	76	68	144

χ^2 6.6 2 D.F. $p < 0.05$

origin but in any case a somatic connection seemed improbable.

A study of recurrent abdominal pain in children between 4 and 6.9 years among the Sevettijärvi Skolts and the Finnish groups reveals no significant difference, but after the age of 7 the frequency of abdominal pain is higher among the Finnish children (Table 33). The higher frequency among the Finnish children can naturally be correlated with a better cooperation at the examination and the fact that the children are more communicative, but it can also be attributed to the greater strain the Finnish children experience under the pressure of school and all that is expected of them.

5. Enuresis

All the children who were reported to have wetted the bed after 4 years of age were recorded as cases of enuresis nocturna.

The frequency can be seen from tables 34 and 35. The rate of enuresis was fairly high among the Sevettijärvi Skolt boys and among the Nellim 1/2 Skolt girls. The rate was not higher among the children living in the school boarding house than among those living at home.

The difference in enuresis frequency between Sevettijärvi 1/1 Skolt boys and Finnish boys is significant ($p < 0.01$). Also for Sevettijärvi 1/1 Skolt girls and Finnish girls there is a significant difference ($p < 0.05$).

That the higher frequency of enuresis nocturna not is due to a lower age among the Skolt children is shown by the fact that the mean age for the 1/1 Skolt boys is 10.1 years and for the Finnish boys 9.7 years. For the girls the ages were 9.8 and 9.1 years, respectively.

TABLE 34

Enuresis nocturna in boys over 4 years of age

	Sevettijärvi		Nellim 1/1 Skolt		Nellim 1/2 Skolt		Sasall + Tanhua Finnish		Total	
	N		N	%	N	%	N	%	N	%
No enuresis	37	(72.5)	13	(81.2)	20	(100.0)	40	(95.2)	110	(85.3)
Enuresis	14	(27.4)	3	(18.7)	0	(0)	2	(4.8)	19	(14.7)
Total	51		16		20		42		129	

χ^2 13.6 3 D.F $p < 0.01$

TABLE 35

Enuresis nocturna in girls over 4 years of age

	Sevettijärvi		Nellim 1/1 Skolt		Nellim 1/2 Skolt		Sasall + Tanhua Finnish		Total	
	N	%	N	%	N	%	N	%	N	
No enuresis	40	(85.1)	13	(92.9)	11	(68.7)	47	(97.9)	111	(88.8)
Enuresis	7	(14.9)	1	(7.1)	5	(31.2)	1	(2.1)	14	(11.2)
Total	47		14		16		48		125	

χ^2 11.4 3 D.F $p < 0.01$

TABLE 36

Encopresis in children over 4 years of age

	Sevettijärvi		Nellim 1/1 Skolt		Nellim 1/2 Skolt		Sasall + Tanhua Finnish		Total	
	N	%	N	%	N	%	N	%	N	%
No encopresis	95	(96.9)	30	(100.0)	35	(97.2)	84	(95.5)	246	(96.8)
Encopresis	3	(3.1)	0	(0)	1	(2.8)	4	(4.5)	8	(3.2)
Total	98		30		36		88		254	

χ^2 1.5 3 D.F $p > 0.2$

6. *Encopresis*

The distribution of the frequency of encopresis among children aged 4 or over is presented in Table 36. The mean age of the youngest Nellim 1/2 Skolt group was 8.9 years. No significant difference was demonstrable between the groups.

Two girls aged 6 had encopresis. One was from Sevettijärvi and the other was a 1/2 Skolt girl from Nellim. All the Finnish children with encopresis were boys, all of Tanhua (encopresis frequency for Tanhua is thus 7.8 %). None of the encopretic

TABLE 32

Abdominal pain. Children over 4 year of age

	Sevettijärvi		Nellim 1/1 Skolt		Nellim 1/2 Skolt		Sanali+Tanhua Finnish		Total	
	N		N		N	%	N		N	%
No pain	78	(82.1)	24	(80.0)	24	(66.7)	65	(70.6)	191	(75.4)
Occasional	16	(18.8)	6	(20.0)	8	(22.2)	18	(19.5)	48	(19.1)
Frequent	1	(1.1)	0	(0)	4	(11.1)	9	(9.7)	14	(5.5)
Total	95		30		36		92		253	

χ^2 11.9 6 D.F $p > 0.05$

TABLE 33

Abdominal pain. Children over 7 years of age

	Sevettijärvi 1/1 Skolt	Sanali+Tanhua Finnish	Total
	N	N	N
No pain	61	45	106
Occasional pain	14	16	30
Frequent pain	1	7	8
Total	76	68	144

χ^2 6.6 2 D.F $p < 0.05$

origin, but in any case a somatic connection seemed improbable.

A study of recurrent abdominal pain in children between 4 and 6.9 years among the Sevettijärvi Skolts and the Finnish groups reveals no significant difference, but after the age of 7 the frequency of abdominal pain is higher among the Finnish children (Table 33). The higher frequency among the Finnish children can naturally be correlated with a better cooperation at the examination and the fact that the children are more communicative, but it can also be attributed to the greater strain the Finnish children experience under the pressure of school and all that is expected of them.

5 Enuresis

All the children who were reported to have wetted the bed after 4 years of age were recorded as cases of enuresis nocturna.

The frequency can be seen from tables 34 and 35. The rate of enuresis was fairly high among the Sevettijärvi Skolt boys and among the Nellim 1/2 Skolt girls. The rate was not higher among the children living in the school boarding house than among those living at home.

The difference in enuresis frequency between Sevettijärvi 1/1 Skolt boys and Finnish boys is significant ($p < 0.01$). Also for Sevettijärvi 1/1 Skolt girls and Finnish girls there is a significant difference ($p < 0.05$).

That the higher frequency of enuresis nocturna not is due to a lower age among the Skolt children is shown by the fact that the mean age for the 1/1 Skolt boys is 10.1 years and for the Finnish boys 9.7 years. For the girls the ages were 9.8 and 9.1 years, respectively.

8 Nail-biting

Children over 4 years of age were included in the statistics. Both the parents and the children were questioned and the nails were inspected. Statistics are presented in Table 38

Nail-biting occurs both among the Skolt children and the Finnish children of Tanhua, with approximately the same frequency as was quoted by Jonsson and Kälvesten (1964) for the Stockholm boys (20.8 %), and by Klackenberg (1971) for children in their first year at school (5 often, 15 % occasionally and 40 seldom)

It is striking that no Finnish child of Sassali was nail biter

9 Motor restlessness and hyperactivity

The parents were asked if they considered the child to be more restless than its siblings or more restless than children in general. If the parents found the child's restlessness and hyperactivity very disturbing the child was classified under the heading »serious restlessness» If restlessness was present but could be tolerated the category was »moderate restlessness» and otherwise »no signs of restlessness»

There were no significant differences between the under 7 year olds of the different groups. The frequency for children over 7 years of age is presented in Table 39

Serious disturbances, not noted among the other children, were seen among the Finnish children. This possibly reflects the greater parental demands made on school children in the Finnish families, but no definite conclusions can be drawn since much depends on the parents faculty of observation and their tolerance towards the restlessness. The frequency in the present material slightly exceeds that recorded by Jonsson and Kälvesten (1964) but it is difficult to make comparisons since the criteria apparently were different

10 Aggressive outbursts

The children's aggressive outbursts were classified according to the parents appraisal as occurring often (once a week or more often) or seldom (less than once a week or once a fortnight)

Table 40 covers only the children over 4 years of age. It is seen that the Finnish children had a slightly higher frequency of aggressive outbursts, especially in the Sassali group in which the parental control was stricter

A comparison of the Sevettijärvi and the Finnish children gives no significant difference in the frequency of aggressive outbursts for children under the age of 7 whereas for children aged over 7 the difference is significant (Table 41) This is perhaps an outcome of the greater parental demands laid on Finnish children.

11 Fear

Children over 4 years of age are included. The things arousing fears were specified as fear of the dark, thunder strangers, animals in general wild animals (which are extremely rare in these districts) ghosts, illness, being alone in the forest being out in a boat when it is windy and of the house catching fire. The mother's replies were supplemented by those of the child, and the occasions when the child listed more fears than the mother knew about were more numerous than the reverse occasions when the child denied being afraid of something that the mother had mentioned Up to three, fears were classified as slight, for more than three as pronounced Table 42 presents the results for the girls.

The difference between groups is statistically significant. The Sevettijärvi and Nellim 1/1 Skolt girls showed more signs of fear than the children who had grown up in 1/2 Skolt and Finnish families.

For boys also there is a statistical connection between the place where they live and the degree of fear (Table 43)

It was remarkable that especially the bigger boys of Sevettijärvi, who had earlier found it difficult to establish contacts and to express themselves during the examination suddenly became lively and opened up when the discussion turned to the things they were afraid of

TABLE 39

Hyperactivity in children over 7 years of age

Signs	Sevettijärvi		Nellim		Nellim		Sanali		Tanhua		Total	
	1/2 Skolt				1/2 Skolt		Finnish					
	N	%	N		N	%	N	%	N		N	%
No signs	71	(93.4)	22	(88.0)	20	(83.3)	27	(90.0)	31	(86.1)	171	(89.5)
Moderate	5	(6.6)	3	(12.0)	4	(16.7)	2	(6.7)	1	(2.8)	15	(7.9)
Severe	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.3)	4	(11.1)	5	(2.6)
Total	76		25		24		30		36		191	

χ^2 17.9 8 D.F $p < 0.05$

TABLE 40

Aggressive outbursts in children over 4 years of age

Signs	Sevettijärvi		Nellim		Nellim		Sanali		Tanhua		Total	
	1/1 Skolt				1/2 Skolt		Finnish					
	N	%	N		N	%	N	%	N	%	N	%
None	55	(58.5)	19	(63.3)	25	(69.4)	11	(28.2)	23	(46.0)	133	(53.4)
Seldom	32	(34.0)	9	(30.0)	10	(27.8)	23	(58.9)	27	(54.0)	101	(40.6)
Often	7	(7.5)	2	(6.7)	1	(2.8)	5	(12.8)	0	(0)	15	(6.0)
Total	94		30		36		39		50		249	

χ^2 23.6 8 D.F $p < 0.01$

TABLE 41

Aggressive outbursts in children over 7 years of age

Signs	Sevettijärvi		Finnish		Total	
	N	%	N	%	N	%
None	44	(58.7)	23	(38.4)	67	(47.5)
Seldom	25	(33.3)	38	(54.1)	63	(44.6)
Often	6	(8)	5	(7.5)	11	(7.9)
Total	75		66		141	

χ^2 8.8 2 D.F $p < 0.05$

TABLE 42

Fears in girls over 4 years of age

	Sevettijärvi		Nellim		Nellim		Sammalli + Tanhua		Total	
	1/1 Skolt				1/2 Skolt		Finnish			
	N	%	N	%	N	%	N	%	N	%
None	13	(29.6)	3	(21.4)	9	(56.3)	24	(52.2)	49	(40.8)
Moderate	23	(52.3)	7	(50.0)	6	(37.5)	10	(21.7)	46	(38.3)
Severe	8	(18.1)	4	(28.6)	1	(6.3)	12	(26.1)	25	(20.8)
Total	44		14		16		46		120	

χ^2 13.9 6 D.F $p < 0.05$

TABLE 43

Fears in boys over 4 years of age

	Sevettijärvi		Nellim		Nellim		Sammalli + Tanhua		Total	
	1/1 Skolt				1/2 Skolt		Finnish			
	N	%	N	%	N	%	N	%	N	%
None	15	(37.5)	11	(73.3)	16	(80.0)	25	(61.1)	67	(57.8)
Moderate	16	(40.0)	3	(20.0)	3	(15.0)	13	(31.7)	35	(30.2)
Severe	9	(22.5)	1	(6.7)	1	(5.0)	3	(7.3)	14	(12.0)
Total	40		15		20		41		116	

χ^2 14.2 6 D.F $p < 0.05$

Thirty-two of the 39 Sevettijärvi children aged over 12 said that they were afraid, whereas only 13 of the 31 Finnish children were referred to the groups with slight or pronounced fears.

This was a registration of what can be called conscious fear or according to Jersild (1966) »irrational fear» It may be assumed that the Skolt culture, with its belief in ghosts and spirits, predisposes for such states of fear among children. This is illustrated by the case of the 13-year old girl who was afraid of ghosts Her father of 61 told in a trembling voice how he had once seen something which he thought at first was the postman's lantern on the ice in the dark, but later when no postman arrived and no tracks could be seen, he realised he had seen a ghost. Or the mother of 47 who said that she always ran very very fast in the forest when she was looking for her reindeer »for you never know what might be there» This mother's son, 11 said he was afraid of ghosts.

12 *An overall picture of the psychosomatic and nervous symptoms*

In order to obtain an overall idea of the children in the various groups, the number of symptoms present per child was counted. Table 44 shows that the mean number of symptoms per group (about 3) is much the same. All the symptoms recorded under the heading of psychosomatic and nervous symptoms were included

TABLE 44

Symptom loadings in individual children

N of symptoms	Sevettijärvi		Nellim		Nellim		Sassali+Tanhua		Total	
	1/1 Skolt				1/2 Skolt		Finnish			
	N	%	N	%	N	%	N		N	
1	22	(19.5)	4	(12.9)	8	(18.2)	16	(14.6)	50	(16.8)
2	11	(9.7)	5	(16.1)	5	(11.4)	19	(17.3)	40	(13.4)
3	31	(27.4)	6	(19.4)	13	(29.6)	23	(21.0)	73	(24.5)
4	22	(19.5)	6	(19.4)	7	(16.0)	21	(19.1)	56	(18.8)
5	13	(11.5)	4	(13.0)	3	(6.8)	13	(11.8)	33	(11.1)
6	8	(7.1)	3	(9.7)	4	(9.1)	9	(8.2)	24	(8.1)
7	3	(2.7)	2	(6.5)	1	([illegible])	6	(5.5)	12	(4.0)
8	2	(1.8)	1	(3.2)	2	(4.6)	2	(1.8)	7	(2.4)
9	1	(0.9)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.3)
10	0	(0.0)	0	(0.0)	1	(2.3)	1	(0.9)	2	(0.7)
11	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Total	113		31		44		110		298	
Mean of symptoms per child	3.3		3.7		3.6		3.8			

TABLE 45

Behaviour in examination situation. Boys

	Sevettijärvi		Nellim		Nellim		Sassali		Tanhua		Total	
			1/1 Skolt		1/2 Skolt		Finnish					
	N	%	N	%	N		N	%	N	%	N	%
Cooperating	14	(26.4)	8	(47.1)	11	(52.4)	14	(77.8)	19	(63.3)	66	(47.5)
Neutral	24	(45.3)	5	(29.4)	8	(38.1)	4	(22.2)	5	(16.7)	46	(33.1)
Negative	15	(28.3)	4	(23.5)	2	(9.5)	0	(0)	6	(20.0)	27	(19.4)
Total	53		17		21		18		30		139	

χ^2 22.7 8 D.F $p < 0.01$

F OVERALL EVALUATION OF THE CHILD

The children's behaviour at the child psychiatric observation or interview for the older children and in the test situation with Oseretsky's motor test was evaluated according to three grades as cooperative, negative or neutral. The frequencies are presented in Tables 45 and 46.

For the girls, there was no significant difference between the groups, whereas among the boys, the 1/1 Skolt boys showed poorer cooperation.

Surprisingly enough the Finnish girls were significantly less cooperative than the Finnish boys ($p < 0.05$). For the Sassali children the difference is not significant whereas the difference in cooperation between the boys and girls of Tanhua is significant ($p < 0.01$).

Within the groups there were of course considerable individual variations. It may be said by way of general appraisal, that

TABLE 46

Behaviour in examination situation. Girls

	Sevettijärvi 1/1 Skolt		Nellim		Nellim 1/2 Skolt		Sassali		Tanhua Finnish		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Cooperating	20	(36.4)	6	(42.8)	11	(57.9)	20	(64.5)	11	(36.6)	68	(45.6)
Neutral	24	(43.6)	4	(28.6)	7	(36.8)	8	(25.8)	17	(56.7)	60	(40.3)
Negative	11	(20.0)	4	(28.6)	1	(5.3)	3	(9.7)	2	(6.7)	21	(14.1)
Total	55		14		19		31		30		149	

χ^2 15.0 8 D.F. $p > 0.05$

it often took quite long to establish a good contact with the Skolt children. They were distinctly less used to cooperating in strange situations and often concealed their anxiety behind capricious, negative behaviour or showed signs of tension: blushed, perspired, and so on. In particular the Finnish children of Sassali gave the impression of being happy, open-natured, and secure even in an unusual situation.

An attempt to get an overall picture of the child's psychic health was made. This included a) the appraisal made by the present author during the child psychiatric observation, b) the loading of nervous and psychosomatic symptoms, c) the appraisal made by the father, d) the appraisal made by the mother. In all these respects a scale from 1—3 points was used, 3 indicating the most severe degree of disturbance. If the mean of these points exceeded 2, the child was considerd as disturbed. For the school-age children, data was available on all these appraisals (a—d) for 31 Skolt girls and 32 Skolt boys from Sevettijärvi, and for 30 Finnish girls and 29 Finnish boys — 16 % of the Skolt girls and 37 % of the Skolt boys, against 23 % of the Finnish girls and 31 % of the Finnish boys, were rated as disturbed.

Discussion

The total number of Skolt Lapps living in Finland is about 600 This was the fact that determined the ceiling limit for the size of the material All children under 15 years of age living in the Skolts main villages of Nellim and Sevettijärvi were examined. Thanks to earlier research among the Skolt Lapps, in sociology geography anthropology and medicine, we know many background factors concerning the Skolt Lapp children, required to complement the present study In order to pinpoint as far as possible, the effects of cultural and genetic factors in the present study the Finnish control material was selected in such a way that the relevant children represented at least the third generation living in major Finnish villages (Sassali and Tanhua) in North Finland Geographically they were situated close to the Skolt districts the children lived in the same climatic, daylight and darkness conditions Road connections with the Finnish villages were also sometimes poor and mostly there were no conveniences such as piped water and electric lighting Owing to the long distances, school boarding houses were necessary for many children among both the Skolt Lapps and the Finns. Families of the Finnish group also lived partly by reindeer herding

The differences between the groups were thus mainly due to the cultural background The traditions of the Skolt Lapps are largely based on the form of life and the practices that developed during the semi nomadic existence while they were living in the Kola Peninsula. This was the time when they also adopted the Orthodox Faith which they have held ever since even though it has had no major influence on the Skolt Lapps ideas and general way of thinking

Serologic studies have shown genetic characteristics in the Skolt Lapps that differ from the serology of the Finnish population. The anthropologic features of the Skolt Lapps distinguish them from other Europeans.

Most families of the Finnish Sassali group were economically well situated the village was an agricultural community and there was no unemployment. Socially the village was characterized by an internal solidarity and the people had little contact with the outer world despite the good transport communications. In many families there was a strict »old time-religious» attitude, and much importance was attached to the children s behaviour and upbringing

In the Finnish district of Tanhua there were often long distances between the families. Half of the children examined lived in a school boarding house during the school term. Unemployment and economic insecurity was more common than in Sassali

Nellim, in addition to the genuine 1/1 Skolt group also had a group of genuine Skolt women married to Finnish men This group in many ways shows the difficulties arising from the attempt to combine two different attitudes of life in this case those of the Skolt culture and the Finnish society The 1/2 Skolts have therefore been treated as a separate group in calculating the results

The social situation of the Skolt Lapp children

Through acculturation the Skolt society of today has lost a great deal of its original character The Skolt Lapps present way of life differs less from that of the North Finnish inhabitants than it did earlier However at the time of the

present study the Skolt community of Sevettijärvi, in particular was characterized by adverse conditions due to a low economic standard, and by geographical and cultural isolation. Reindeer herding and fishing which used to be the main livelihoods of the Skolts, no longer have the same economic importance The natural conditions required for this work have deteriorated. The Skolt Lapps now obtain a part of their subsistence from forest work, road construction etc. The chances of finding well-paid work are slender especially in Sevettijärvi even for persons with a good school education. Many of the generation who are parents today have themselves had little school education more than half the number had a maximum of 1—2 years in primary school. This generation, for obvious reasons, feels little motivation to encourage their children in their school education. This is manifested in the Skolt children's poorer motivation for school attendance, and a poor performance in relation to their intellectual capacity The parents of the Finnish families of Sasali had usually passed through at least six years of primary school which also was the case with the Finnish mothers in Tanhua whereas in Tanhua most fathers had only done 2 years. The Finnish children in Sasali showed the greatest interest for school work.

Poor economy and ill health of the parents, especially the mothers, produced difficulties in the homes. This was a contributory factor towards explaining the fact that more Skolt children than Finnish children of the control group had spent a minimum of six months at a children's home, usually because the mother had been ill. Owing to the long distances between school and home, many children had to stay in the school boarding house during the term from the age of 7 onwards with home visits only during the longer holidays at Christmas, Easter and in the summer The Lapps traditionally have close family ties, and the children had previously been taught mainly by imitating their parents in the home. The transition to the present school system therefore involved considerable changes both for the children and their parents. The children had to exchange the freedom of a life in close contact with nature for that of the crowded classrooms. Moreover instruction was given in Finnish, which was a foreign language for many 7 year old children whose mother tongue was Skolt Lappish. Life in the boarding house where the regime often differed from the child-centred permissive atmosphere at home, produced negative reactions in many children, particularly at the beginning On the other hand many parents were relieved to have the children at boarding-school, where they were given regular meals, especially if the family was large and food scarce

The state of physical health

The rate of somatic illness was highest in the Sevettijärvi group in which half the children had suffered from a manifest disease. Ear and other infections were common, as is the case with all populations in the Arctic Regions. In spite of this, the mean erythrocyte sedimentation rate among the children of Sevettijärvi did not exceed that of the Finnish children.

The dental status can be considered an indication of the state of somatic health and the standards of the individual care of health The incidence of caries was high among the Skolts and 1/2 Skolts, and in the Finnish children of Tanhua, whereas the Finnish children of Sasali on the whole had good teeth In Sasali, the contributory factors to this good result apparently were the strict discipline and abstention from sweets.

The growth of the Skolt children, in both height and weight, is below that of the Finnish children This applies particularly to the children of Sevettijärvi where the economic standing was lowest and the nutritional conditions were poorest. The difference was particularly pronounced in the Skolt boys. This supports the assumption that boys less successfully than the girls withstand the rigours of an unfavourable environment (Greulich 1957 Graffar and Corbier 1966)

The state of psychic health

The state of psychic health among the Skolt children was much the same as in the Finnish control groups. All groups showed an average of about three nervous symptoms per child and the number of disturbed children was approximately the same in every group. A distinct difference however was noted in that the lowest proportion of disturbed children in school age (16 %) was found among the Skolt girls, the highest (31 %) among the Skolt boys. The percentages for the Finnish children were 23 % for the girls and 31 % for the boys.

It often took a long time with the Skolt children, especially the boys, to make a good contact. They were clearly unused to cooperating in strange situations and often concealed their anxiety behind a capricious negative behaviour or showed signs of tension, perspiration, blushing etc. On the other hand the Finnish children of Sassali gave the impression of being gay, open and secure even in a strange situation. It is striking however that the Finnish girls of both the Sassali and Tanhua groups showed poorer cooperation than the Finnish boys.

In contrast to these relatively well adjusted Skolt girls the grown up women in Skolt society seem to be under greater pressure than the men. The percentage of somatic illness among the interviewed mothers was higher than among the Finnish mothers; the latter were all in good health. For the fathers illness was more frequent among the Finns than the Skolts, and this applies especially to the Sassali group. This could indicate that the situation in the Skolt community is the reverse to that in the Finnish society: men carry a heavier burden in Finnish society than women.

The parents' attitude to upbringing and special characteristics among the children

The Skolt upbringing, in general, can be considered to satisfy the child's oral needs in infancy and preschool age. The mothers usually found it important to adapt their ambitions to the child's level of maturity, for instance in toilet training, more so than the Finnish mothers. The upbringing can be described as permissive and free, but the parents used corporal punishment just as much as the Finnish parents. This refutes the assertion in the earlier literature that corporal punishment is not practised among the Lapps. The Skolt Lapp women married to Finns, and consequently under pressure from two cultures, used even severe corporal punishment significantly more often than Finns and the genuine Skolt groups.

The parents were felt to be more accepting, more positively involved and ready to allow more freedom by the Skolt than by the Finnish children. The Skolt children also felt their parents were more comforting, helpful and happier to be together with their children, than the Finnish children found their parents. The difference was significant for the girls and showed a tendency to significance for the boys. This emotionally good relationship provides a good foundation for the Skolt children's positive identification with their parents.

Interviews with the parents disclosed no major differences between the groups concerning attitudes towards the children (warm, neutral, cool). It is striking, however, that four Finnish mothers but no single Skolt or 1/2 Skolt mother were evaluated as overprotective. This result runs parallel with those obtained on examining the children. Three of these Finnish mothers were gainfully employed outside the home, and the fourth was not out at work but was highly extrovert and often away from home. The material is small but gives rise to speculations as to whether the fact that these women had given up the traditional role of being simply and solely a homekeeper had affected their attitude towards the children.

The Skolt mothers have apparently retained a more natural protective instinct towards their children, although the child mortality rate among the Skolts is higher than among the Finnish population. The size of the family has not influenced this attitude since the number of children per family was largely the same among Skolts and Finns. Only in the Nellim 1/2 Skolt

ıp was ıt lower apparently because of mothers lower mean age, as a result of ch the families had not yet reached ır final size.

This group naturally also had the atest number of really wanted child ı, whereas the Sevettijärvi and Tanhua oups with large families and lower onomic standing more often described e child as less welcome.

On the other hand, the Skolt mothers sitive attitude towards their daughters d to the result that most girls, especially nong the Nellim 1/1 Skolt children ere attached to the mother The diffe- ence was statistically significant.

In the young families of the Nellim /2 Skolt group the children, as indicated vere usually welcom The mothers, how ver were apparently uncertain of their own position between the two cultures, of their role as mothers and which culture s attitude towards upbringing they should choose. As a result, the children s attach ment to both parents was remarkably fre quent. In no other group was the percent age of children with the closest attach ment to mother so small as in this group

This could indicate that the Nellim 1/2 Skolt children to a greater extent wish to identify themselves with the culture of the surrounding Finnish majority and that their feeling for their mother s Skolt culture therefore is less pronounced.

The Skolt children are confronted with a new unaccustomed situation when they begin school. This might be expected to cause an accumulation of nervous symptoms in Skolt children over 7 years of age The study showed however that the frequency of recurrent abdominal pain, which can be interpreted as psychogenic in origin is significantly lower among the Skolt than among the Finnish school children, as are also motor restlessness and hyperactivity This is apparently because the Skolt parents are less ambitious for their children to do well at school, at home, there is less pressure on the child about his schoolwork. Naturally it may also reflect the Finnish parents higher standards of behaviour where bigger children are concerned These parents have less tolerance for symptoms such as motor restlessness.

The school aged Skolt children showed also a significantly lower frequency of aggressive outbursts than the Finnish children Aggressions are seldom seen in the Skolt culture and are not well tolerat ed. When the children were punished it was usually for aggressive behaviour such as quarrelling between the siblings Adults usually dislike quarrelling and are asham ed of it (Pelto 1962) Quarrelling between the married couples was also less common in the Skolt families than in the Finnish families. This could presumably be a relict from the days when external condit ions were so difficult that the struggle for existence left no time or energy for qua relling within the group or family

Old ideas of supernatural beings still survive more or less subconsciously in the Skolt culture, especially among the older parents of the children examined. This predisposes the children to feelings of fear which is manifested in the signifi cantly higher frequency of symptoms of »irrational fear» among the Skolt than among the Finnish children over 4 years of age

The finding that anorexia among Skolt children is less frequent than among the Finnish children surely is less dependent on the parents educational attitudes than on external factors. The children with no appetite were fewest among the Sevetti järvi Skolts, the group which on the aver age has the greatest economic difficulties and which sometimes may even suffer from a lack of food. The result confirms the earlier observations according to which anorexia is a symptom typical of a welfare society

Other special features connected with Skolt culture

In the Skolt culture a large proportion of the upbringing is based on imitation. The children, who are constantly roaming the forest and fells, are trained to use their powers of observation. This is clearly shown e.g by the psychological tests in which the Skolt children were significantly better than the Finnish children, viz.

those requiring the faculty of observation.

In the so-called »culture bound tests» especially the verbal tests the Skolt children showed significantly poorer results. This may in part be attributed to the Skolts bilingualism and in part to the cultural conditions as well as to the fact that the Skolt children were less used to dealing with the kind of tasks given them in the test.

This agrees with MacArthur's (1973) observations concerning Eskimo children who showed relatively good results in tasks involving the spatial field independence group of abilities and the greatest weakness in the verbal educational group of abilities compared with their White age mates. As predicted by Witkin (cit. MacArthur) in his differentiation theory hunting ecology and upbringing encouraging independence foster relative strength in spatial-field independence abilities. That the perception is dependent on cultural background and early experience is shown also by Myambo (1973) in her experiences concerning »shape constancy» among Europeans and West Africans.

The Skolt children, especially the boys, spend a lot of time out of doors, become accustomed, while they are still young to walk to the fishing places, they accompany their fathers to the reindeer herds, cover long distances to school, etc. One would expect therefore, that their motor skills would be superior to those of the Finnish children. The girls display a tendency towards better results in Oseretsky's motor test but the difference is not significant. Surprisingly enough, the Sevettijärvi boys showed a significantly poorer result than the Finnish boys and girls and the Sevettijärvi girls. The result is significant even if the children with a negative attitude towards the investigation are excluded from the statistical calculations.

An explanation for this might be found in the socio-economically inferior conditions in which the Skolt children grow up. According to Greulich (1959) and many other authors, factors of this type affect the boys more since they are more sensitive to the less favourable environmental conditions, such as nutritional conditions. These could be presumed to cause neuro-physiological immaturity and poorer motor skills. This observation also agrees with Espenschade's (1940) statement according to which motor skills in boys are correlated with emotional and physiological maturity and the Skolt boys showed other signs of emotional and physiological immaturity i.a., poorer cooperation and slower growth.

Are there genetic aptitudes of importance for Skolt children?

No genetic diseases were demonstrated in studies of adult Skolt individuals (Henrik Forsius et al 1966). Nor were any signs of particular disease producing genes found among the children. However nocturnal enuresis was significantly more frequent than among the Finnish children. The etiology of enuresis is heterogeneous but according to Hallgren (1957) there is a group of genetically dependent cases in which the manifestation of the genes is determined by environmental factors. This is the most easily acceptable interpretation concerning the rate of enuresis among the Skolts. The environmental factors in this case would be, primarily the adverse conditions which accompany the low economic standing (v. Harnack 1953) and which in the present case also proved to affect the boys more than girls. The ratio between girls and boys was 1 1.3 which agrees with other study results reported (Klackenberg 1971 and others). A familial occurrence of enuresis was noted in four of the Sevettijärvi families 2 children of one family three children each of two families, and all the 6 boys of one family had been or were night-wetters. The Nellim 1/2 Skolt group contained a family with two enuretic girls. All other cases of enuresis were sporadic in the other groups.

The possibility that the Skolt mothers more permissive toilet training may have affected the frequency of enuresis is naturally not excluded. The fact that during the school terms, a large proportion of the Skolt children live in the boarding house did not affect the issue, since there was no difference in the frequency of enuresis between the children living at

home and those living in the boarding house.

The cases of enuresis among the Finnish children were evenly divided between the Sassali and the Tanhua groups. The tendency towards a more permissive toilet training among the Tanhua mothers, in contrast to the Sassali mothers attitude which was the strictest of all, did not affect the issue.

In conclusion, it should be borne in mind that the Finnish population in the North has been settled there for a long time, and any changes towards a more »modern» society have taken place relatively slowly whereas the Skolt population were still semi nomads one generation ago. The change-over to a settled existence involved radical changes in their way of life and in their ways of thinking. Furthermore, Skolt communities have been subjected to geographical transpositions, a situation in which a readjustment of an individual's whole conception of life is more liable to take place than if he had remained in his old surroundings. Pelto (1962) recalls the fact that the Skolts no longer live in their old and wellknown environment where a given contour in the landscape was associated in the imagination with supernatural beings and where their ancient Skolt places of worship are situated. These changes may in part, be the reason why belief in the old superstitions is declining more rapidly. The modern Skolt is not prepared to admit, at any rate not openly that he believes e.g. in »seitas» or that he worships other nature spirits.

Although many genuine features of Skolt culture have been preserved and give a distinctive character both to the parents valuations and the children's psychological behaviour (Seitamo 1973) it was striking to note the many similarities between the Sevettijärvi group and the Finnish Tanhua group. These localities are very much the same in their socio-economic conditions and geographical isolation. The similarity was in many cases greater than between the two Skolt groups or between the different Finnish groups. The Finnish Sassali group, especially was different from the others, both in respect of the parents state of health, their school education, and their upbringing and in respect of the children's behaviour.

In other words, according to the present study the external factors, ecology along with cultural factors seem to be of great importance for the parents attitudes to upbringing and is reflected in the children's outward behaviour. This conclusion agrees with the views advanced by B. Whiting (1963).

However the phenomena involved, the attitudes towards upbringing and the personality development, are of such a complex nature that it is impossible to draw the line between cause and effect in their interaction, and the result is likely to be a vicious circle.

Summary

There is in North Finland a homogeneous population group the Skolt Lapps, who have long lived in relative isolation. Since this group has its own distinctive culture, it has been considered worth while to make an investigation into whether the children in this group had somatic or psychic characteristics or deviations distinguishing them from other North Finnish children, and whether these disagreeing features — if any — depended on the particular environment in which the Skolt children had grown up including the parents attitudes to upbringing or whether there were genetic aptitudes of importance for the development of Skolt children. This population has been studied by researchers from different branches i.e. geography anthropology sociology and medicine, for which reason a lot of background factors about the children are known.

All children under 15 years of age in the Skolts main settlements in Sevettijärvi and the Nellim district were examined The 28 families of Sevettijärvi had a total of 113 children, and the 9 Nellim families a total of 31 children

Interviews were conducted with 34 Skolt mothers and 29 Skolt fathers. In addition, 44 1/2 Skolt children with purely Skolt mothers and Finnish fathers were examined They belonged to 13 families in Nellim. All 13 mothers and 4 of the Finnish fathers were interviewed The control series consisted of 50 Finnish children of 12 families in the village of Sasali and 60 children of 16 families in the village of Tanhua in North Finland. 27 Finnish mothers and 22 Finnish fathers were interviewed. The Finnish children lived in similar geographical, climatic and socio-economic conditions to the Skolts. The dissimilarities between the groups were therefore mainly related to the cultural and genetic background

The parents were interviewed both concerning their own background and attitudes and also each child s development and psychic health The information obtained was supplemented by data from the children s health cards The children were examined by means of child psychiatric observation, special psychological tests for the evaluation of the developmental level and by projective tests. Oseretsky s test for motor proficiency was carried out on the schoolchildren. All the children underwent a clinical somatic examination

The results disclosed that the state of psychic health among the Skolt children corresponded to that among the Finnish children. An average of three nervous symptoms per child were recorded in all the groups. The number of disturbed children was approximately the same in all groups, although among the school age children there were fewer disturbed Skolt girls (16 %) than Skolt boys (34 %) Among the Finnish school age children, 23 % of the girls and 31 % of the boys were disturbed. The frequency of children with a low intellectual level was largely the same among the Skolt and the Finnish children.

The Skolt children appeared to have less motivation for attending school and a significantly poorer verbal capacity possibly due partly to bilingualism and partly to cultural deprivation In tests requiring a faculty of observation the Skolt children obtained better results than the Finnish children. This reflects the influence of the Skolt culture the Skolt children are used to learning by imitation and to exercising the faculty of perception.

Of the nervous symptoms, loss of appetite was less common among the Skolt

than among the Finnish children a finding assumed to indicate the role of the economic situation in giving rise to this symptom. Motor restlessness and hyperactivity aggressive outbursts of emotion, and recurrent abdominal pain in children of school age were significantly less frequent among the Skolts. Sleep disturbances, headache, encopresis, thumb-sucking and nail-biting had the same frequency among the Skolt and the Finnish children. The Skolt children showed a higher frequency of »irrational fears» which was interpreted as an indication that the Skolt culture, with its remnants of the old conceptions, predisposes its subjects to feelings of fear

Enuresis nocturna was significantly more frequent among the Skolt children with familial accumulations. It was interpreted as indication of a genetic aptitude which becomes manifest through external conditions. Another sign of neurophysiological immaturity among the Skolt boys was the significantly poorer result they showed in Oseretsky's motor test, both compared with Finnish schoolboys and -girls and with Skolt girls of school age. Together with the finding that the Skolt boys growth curve is lower than that of the Finnish children and of the Skolt girls, this supports the opinion according to which boys are more sensitive to negative environmental factors, such as a poorer food supply than girls.

Otherwise, no special diseases that could be attributed to genetic aptitudes could be shown in the Skolt children

The state of somatic health of the Skolt children was inferior to that of the Finnish children.

The Skolt parents way of bringing up children is more flexible and permissive than that of the Finnish parents and pays more attention to the child s degree of maturity when making demands on him, e.g in regard to toilet training The Skolt parents give their children a good »basic trust» and the prerequisites for a positive identification. This facilitates the Skolt children s adaptation to the pressure imposed on them by growing up in a minority culture with its distinctive characteristics, while at the same time the culture of the surrounding Finnish majority increasingly makes itself felt in the demands of education and school performance.

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ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 240 197[illegible]

REARING OF NON IDENTICAL TWINS WITH LYMPHOPENIC HYPOGAMMAGLOBULINAEMIA UNDER GNOTOBIOTIC CONDITIONS

EDITED BY W M. TELLER

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM

I INTRODUCTION

In recent years the diagnosis of immune insufficiency states has shown rapid expansion A great number of various diseases could be classified according to the immune system involved (for review see Fudenberg et al 1971)

The therapy of these conditions however has been much less satisfactory Except for mere replacement of humoral antibodies the restoration of functional immunity has been successful in a few instances only where transplantations of bone marrow from HL A identical donors were performed (Meuwissen et al 1971)

The following report is the account of our experiences in raising a pair of non-identical male twins who suffered from lymphopenic hypogammaglobulinemia They were protected from infections by maintenance in isolators under gnotobiotic or germfree conditions over a period of 2 1/? years.

Our attempts at restoration of their immunity by transplantation of bone marrow in one twin and fetal thymus in the other have been published previously (Flad et al 1971 *a*)

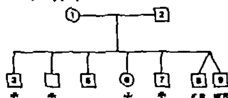
II CASE REPORTS

Family History (Fig 1)

Since the age of 14 years Mrs R now 30 years old suffered from Jacksonian type epilepsy In recent years she has been treated with diphenylhydantoin sodium Her husband, 34 years of age is an alcoholic He was previously gastrectomized because of gastric ulcer Grandparents and parental siblings were not afflicted with apparent hereditary or chronic diseases

The first child of the family a boy died of unknown cause at the age of 6 months He had chronic diarrhea and dermatitis from the age of 2 months through 4 months The second child, a boy died at the age of 9 months of septicemia caused by aerobacter (pyocyaneus) He had con omitant pneumonia, bilateral otitis media and multiple skin abscesses He had been hospitalized for 5 months but did not respond to the usual treatments The third child was a healthy boy who is now 7 years of age The fourth child, a girl was supposedly healthy for 4 months. At the age of 5 months she died of interstitial pneumonitis after 10 days of hospitalization.

The fifth child a boy died at the age of 7 months in another university hospital of interstitial pneumonitis and bilateral otitis At autopsy the thymus and all lymph nodes were markedly hypoplastic For the first time the



Clinical and pathological findings in Family R

Subject No.	General data	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
1	Jacksonian epilepsy							
2	alcoholic							
3		6 mo.	+	?	?	?	?	?
4		9 mo.	+	(+)	↓	↓	↓	?
5	living and well							
6		5 mo.	+	(+)	?	?	↓	?
7		6 mo.	+	+	↓	↓	↓	↓
8	present cases							
9								

Signs and symptoms
no healthy
+ frequent severe/marked
? not known
↓ markedly decreased
– definitely absent
(+) slight

Fig 1 Pedigree of Family R. and disease states of various members.

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ACTA PÆDIATRICA SCANDINAVICA
SUPPLEMENT 40, 1973

From the Departments of Pædiatrics, Internal Medicine and Clinical Physiology, University of Ulm, Ulm/Donau, F. R. Germany

REARING OF NON-IDENTICAL TWINS WITH LYMPHOPENIC HYPOGAMMA-GLOBULINAEMIA UNDER GNOTOBIOTIC CONDITIONS

edited by

W. M. Teller

in collaboration with

U. Genscher, W. M. Teller – Clinical Care
H. D. Flad, G. Hochapfel, R. P. Huget – Immunology
M. Dietrich, D. Krieger, R. Wilson – Gnotobiotics and Microbiology
K. Kohle, C. Simons – Psychology
T. M. Fliedner, F. Trepel – Clinical Physiology

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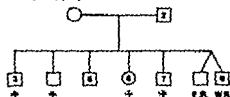
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The fifth child a boy died at the age of 7 months in another university hospital of interstitial pneumonitis and bilateral otitis. At autopsy the thymus and all lymph nodes were markedly hypoplastic. For the first time the



Clinical and pathological findings in Family R

Subject No	General state	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	intermittent epilepsy							
2	alcoholic							
3		mo.		?		?	?	?
		mo.	+	(+)	↓	↓	↓	?
5	living and well							
6		5 mo.	+	( )	?	?	↓	?
7		mo.		+	↓	↓	?	↓
8	present cases							
9								

Signs and symbols mo. months
\+ frequent severe / marked
? not known
↓ markedly decreased
definitely absent
(+) slight

Fig 1 Pedigree of Family R nd disease states of ariou members

diagnosis of congenital immunodeficiency was established

Early history and findings

Following her sixth pregnancy which was entirely uneventful Mrs R. was delivered of dichorionic male twins The first twin (E R) was born in occipital position with an Apgar score of 10 The second twin (W R.) was delivered from breech presentation His Apgar score was 9 Following birth the twins were transferred to the Department of Pediatrics University of Ulm/Donau

Physical findings

On admission at the age of 4 hours their physical findings were as follows

E. R. Well developed male infant with all signs of maturity Weight 2 320 g, length 47 cm Lungs expanded normal heart sounds liver and spleen not enlarged Regular muscle tone normal reflexes X-ray chest no apparent thymus (Fig. 2)

W R. Well developed male infant with all signs of maturity Weight 2 980 g length 49 cm. Lungs expanded normal heart sounds liver and spleen not enlarged Normal muscle tone normal reflexes X-ray chest Mediastinal shadow widened however on lateral view no apparent thymus (Fig. 3)

Laboratory tests

Peripheral lymphocyte counts of both twins were less than 2 000/mm³ Both had a marked eosinophilia of 600–3 000/mm³ Repeated bone marrow aspirations showed a slightly increased number of lymphocytes no plasma cells were found Serum complement levels were normal Direct Coombs test and LE cell test were negative

Leucocyte typings were performed in the laboratories of Ulm Leiden (Prof J J van Rood) and Geneva (Dr M Jeannet) The results including typing of blood groups were as follows

	Blood groups	Leucocyt groups	Chromosomes
Father	O CcDEe	9 –/2 7	AB
Mother	A.C DEe	9,R /2,8	CD
E. R.	A,CCDee	2 7/2,8	BD
W R.	A.CCDee	9–/7,8	AD

III DIAGNOSIS

Tests for Cell-mediated Immunity

1 *Skin tests*

Primary sensitization was performed with 10% dinitrochlorobenzene (DNCB) in acetone 2–3 weeks later challenge doses of 0 01% DNCB were applied to the volar surface of the forearm and the skin reactivity read 24 48 and 72 hours later

Skin testing of the immunological memory was performed with the following antigens Tuberculin GT (Behringwerke Marburg) 1 10 000 1 1 000 1 100 Candida extract (Hollister Stier) Mumps antigen (Hollister Stier) Coccidioidin (Hollister Stier)

Skin grafting

Full-thickness skin grafts of 2 cm diameter were performed Leucocyte typing revealed a histoincompatibility of 3 antigens between donors and recipients

3 *Lymphocyte cultures*

Heparinized (5 units per ml) blood was sedimented by addition of 1/5 volume of 5% dextran (MW ‿50 000 Pharmacia) in saline The leucocyte rich plasma was centrifuged and washed twice in minimum essential medium (MEM S Grand Island) containing penicillin (50 units/ml) and streptomycin (50 μg/ml)

Table 1 *Humoral Immunity of E R (1st twin) and W R (2nd twin) and of an immunologically healthy control child of the same age*

	Twin E. R.	Twin W R.	Control
1 Tetanus antigen[a]			
a) primary response	<0 01	<0 01	<0 01
b) secondary response	<0 01	=0 01	>0 1
2 Polio antigen type II[b]			
a) primary response	/	/	/
b) secondary response	/	/	/[m]
3 Immunoglobulins[c]			
5th month			
IgG	540	210	427±186
IgA	74	5	28± 18
IgM	10	6	43± 17
10th month			
IgG	420	235	661±219
IgA	78	10	54± 23
IgM	10	10	77± 18
IgE[d]	3 523	400	91± 40
4 Isohaemagglutinins	–	–	+
5 Plasma cells (bone marrow)	–	–	+

[a] I U per ml [c] mg/100 ml
[b] Titres [d] ng/ml

After resuspension in culture medium (MEM S 20% inactivated foetal calf serum penicillin and streptomycin and 1% 200 mM l-glutamine) the cells were passed through a glass column filled with nylon wool to obtain a suspension of 85–98% pure lymphocytes (Flad et al 1971 *b*) Cultures were set up in triplicates at 10^6 lymphocytes in 1 5 ml culture medium and phytohaemagglutinin (PHA) (Burroughs Wellcome) or antigens were added at optimal concentrations as determined previously in 10 normal individuals Cultures were maintained in a moist atmosphere of 5% CO_2 in air harvested after addition of 0 06 μCi of 2-14C thymidine (spec activity 35 6 mCi/mMol) for 16 hours and processed for liquid scintillation counting The stimulation index was expressed as counts per minute per culture with PHA or antigen divided by the counts per minute per culture in control cultures

Tests for Humoral Immunity

1 Immunoglobulins and complement (C3) Partigen plates Behringwerke were used
2 Antibodies to tetanus were determined in a toxin neutralization test to polymerized flagella antigen by passive haemagglutination to polio vaccine by a virus neutralization test

Results

The diagnosis was established by 3 criteria 1) family history 2) cell-mediated and 3) humoral immunity Fig. 1 shows that the twins had 4 male and female siblings who died from

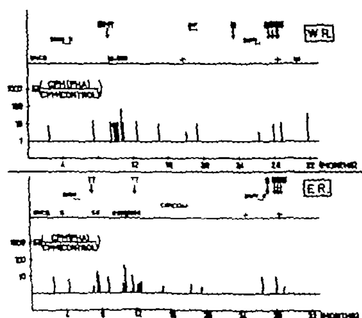


Fig 4 Cell-mediated immunity in E. R and W R. BMT = bone marrow transplantation TT = thymus transplantation R = rejection of skin graft BIF = Bifidus bacteria, B = implantation of bacteria S = implantation of stool. *In E. R.* A slight rise of the lymphocyte stimulation index after TT is observed. *In W R* Note the transient rise of the lymphocyte stimulation index and the positive DNCB test after BMT and after B

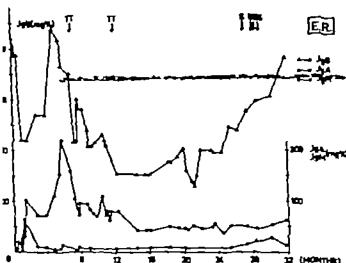


Fig 5 Serum immunoglobulin levels in patient E. R. For abbreviations see Fig. 4 At 4 to 5 months of age the infant was out of the isolation at which time a rise of IgG and IgA was noted Implantation of a bacterial intestinal flora resulted in a rise of IgG

Table 2 *Cellular immunity of E R (1st twin) and W R (2nd twin) and of an immunologically healthy control child of the same age*

	Twin E. R.	Twin W. R.	Control
DNCB skin test	–	–	+
Rejection of first-set skin homograft	>13 days	>13 days	Not done
Rejection of second-set skin homograft	21 days	18 days	Not done
PHA-response of lymphocytes			
a) Transformed cells (%)	34	41	84
b) ^{14}C-thymidine incorporation ratio (DPM × 10^{-3})	3 600	5 300	15 000
One way stimulation test (lymphocyte stimulation by allogeneic cells)	Decreased	Decreased	Normal

severe infections within the first year of their lives. In two siblings pathologic-anatomical examination of the lymphoid organs revealed a decreased content of lymphocytes in spleen lymph nodes and thymus One sibling was healthy Both parents were immunologically normal and gave no evidence of immune deficiency

Cell mediated immunity in both infants is characterized by a lack of sensitization to DNCB a retarded rejection of a primary and secondary histoincompatible skin graft and a decreased ability of lymphocytes to respond in vitro to PHA and allogeneic cells (Fig. 4 Table 2) The stimulation index was usually



Fig 6 Serum immunoglobulin levels in patient W R. For abbreviations see Fig. 4 A sharp rise of IgG is noted after BMT After implantation of a bacterial intestinal flora IgG IgM and IgA levels rose

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	Twin E. R.	Twin W. R.	Control
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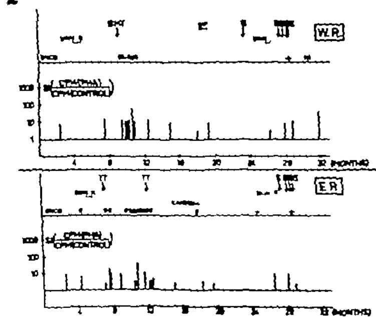


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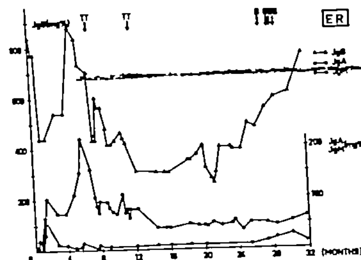


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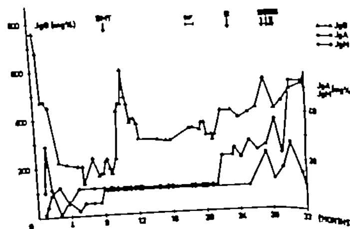


Fig. 6 Serum immunoglobulin levels in patient W. R. For [illegible] tions see Fig. 4. A short [illegible] h noted after BMT [illegible] lation of a bacteria[illegible] IgG, IgM and IgA [illegible]

Act [illegible]

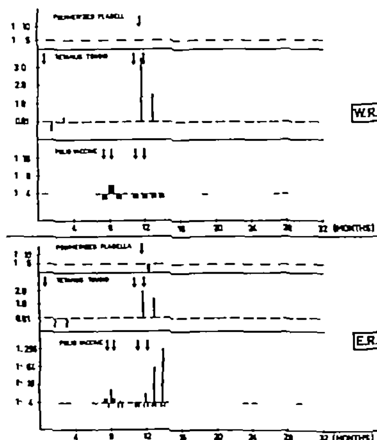


Fig 7 Antibody production in patient W R. and E. R. Dotted lines give the titres above which a reaction is considered to be positi e. A single injection of polymerized flagella antigen did not induce antibody production in both infants Antibodies to tetanus toxoid were higher in patient W R. than in patient E. R. but only positive after repeated immunizations E. R responded only to polio vaccine type II whereas W R. did not respond at all

bout 10 and rose only transiently (see above) The stimulation index in normal individuals n our laboratory is between 700 and 800 Humoral immunity was found to be impaired as evidenced by low levels of serum immunoglobulins IgG IgA and IgM (Fig. 5 6 Table I) The ability of both infants to produce antibodies against tetanus toxoid polio vaccine and polymerized flagella was reduced and was expressed only after repeated immunizations (Fig. 7) Isohaemagglutinins to blood groups A and B were negative for a long period of time.

By these criteria the immune deficiency syndrome in these twins was described as an impairment but not complete absence of both cell mediated and humoral immunity The syndrome belongs to the unclassified group of immunodeficiency diseases according to the recent classification (Fudenberg et al 1971)

IV CLINICAL COURSE

Before isolation

During the second week of life in both twins physiological jaundice appeared with maximal bilirubin levels around 13 mg per 100 ml Despite optimal nursing care E R. acquired a purul n d rmatitis at the same time Staphylococcus albus was cultured from the lesions.

In the fifth and sixth week of life both children suffered from hemorrhagic diarrhea. Besides normal bacteria no pathologic organisms could be cultured from stool specimens. Urinalyses remained normal

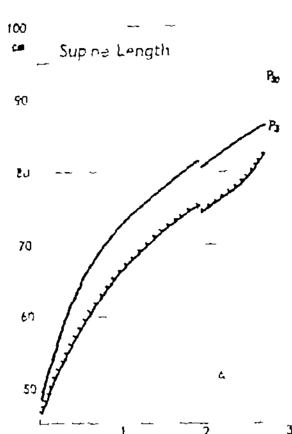


Fig 8 Development of length — W R. ⊥⊥⊥ E. R

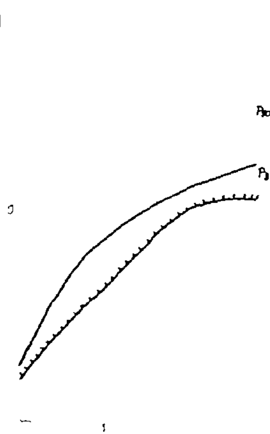


Fig 9 Development of weight — W R. ⊥⊥⊥ E. R

Treatment was initiated with antibiotics and fungistatics Also the skin was washed several times daily with antiseptics. This regimen was started both in order to cope with the enteritis and to decontaminate the children.

During isolation

At the age of six weeks the twins were transferred into isolators especially designed to provide a germfree environment and to ensure bringing up under gnotobiotic conditions (see below) The antibiotic and fungistatic medications were continued with only short intervals throughout the isolation period of almost 30 months. From the beginning of isolation no serious infections occurred. At age 4 months W R showed a maculopapular generalized rash which lasted for six days Temperatures during this period spiked up to 40.3°C The blood culture revealed a gram-negative germ which could not be definitely identified

At the age of 4 months E. R. suffered a convulsive seizure following tetanus toxoid stimulation. He had to be removed from the isolation tent for about 20 days. At age 11 months he revealed *microhematuria* (20–600 *erythrocytes per mm*³) *and proteinuria* (497 mg per 100 ml) No clinical symptoms were apparent and the child continued to thrive The cause of these symptoms remained unexplained

Feedings consisted of sterile adapted pre

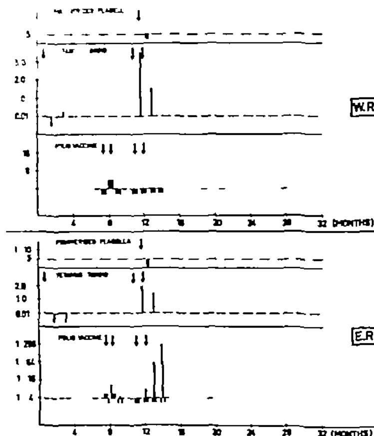


Fig 7 Antibody production in patient W R. and E. R. Dotted lines give the titres above which a reaction is considered to be positive. A single injection of polymerized flagella antigen did not induce antibody production in both infants. Antibodies to tetanus toxoid were higher in patient W R. than in patient E. R. but only positive after repeated immunizations. E. R. responded only to polio vaccine type II whereas W R. did not respond at all

about 10 and rose only transiently (see above) The stimulation index in normal individuals in our laboratory is between 200 and 800 Humoral immunity was found to be impaired as evidenced by low levels of serum immunoglobulins IgG IgA and IgM (Fig 5 6 Table 1) The ability of both infants to produce antibodies against tetanus toxoid polio vaccine and polymerized flagella was reduced and was expressed only after repeated immunizations (Fig. 7) Isohaemagglutinins to blood groups A and B were negative for a long period of time

By these criteria, the immune deficiency syndrome in these twins was described as an impairment but not complete absence of both cell-mediated and humoral immunity The syndrome belongs to the unclassified group of *immunodeficiency diseases according to* the recent classification (Fudenberg et al 1971).

IV CLINICAL COURSE

Before isolation

During the second week of life in both twins physiological jaundice appeared with maximal bilirubin levels around 13 mg per 100 ml Despite optimal nursing care E R. acquired a purulent dermatitis at the same time Staphylococcus albus was cultured from the lesions.

In the fifth and sixth week of life both children suffered from hemorrhagic diarrhea. Besides normal bacteria no pathologic organisms could be cultured from stool specimens Urinalyses remained normal

cell-mediated immunity lymphocytes of the thymus and of the recipient were typed for leucocyte antigens However neither in the peripheral blood of the recipient nor in PHA cultures lymphocytes with the marker antigen 4 a of the donor could be found which suggested that a humoral thymic factor was operative in improving the PHA responsiveness of recipient lymphocytes.

In the later course the child developed a localized infection of the skin with candida albicans Skin tests with candida extract were positive but lymphocytes did not respond to candida antigen in vitro Furthermore no activity of migration inhibitory factor could be detected in lymphocyte culture supernatants when tested on guinea pig peritoneal exudate cells

A skin graft transplanted at the age of 26 months was rejected within 12 days PHA responsiveness of the lymphocytes remained low Implantation of bacteria in the gastrointestinal tract was followed by a marked rise of the IgG level whereas IgA and IgM rose only slowly

Second twin (W R)

As previously reported in twin W R. a transfusion of a concentrate of stem cells derived from maternal bone marrow was performed (Flad et al 1971 *a*) Fig 5 shows a sharp rise of IgG levels following this treatment Unfortunately the genotype of the immunoglobulins could not be determined since there was no difference between the mother and the child Cell mediated immunity was only transiently improved. The DNCB test was positive on one occasion and the response of lymphocytes to PHA was enhanced compared with that before transplantation (Fig. 4) In the later course the DNCB test was repeatedly positive A skin graft transplanted at the age of 26 months was rejected after 14 days When bacteria were implanted the PHA response was somewhat increased but did not reach normal values Furthermore introduction of bacteria resulted in a rise of IgG IgA and IgM levels and isohaemagglutinin titres against blood group B antigen of 1 8 were found

VI GNOTOBIOTIC CARE

General Outline

The dominant role of infections not only by pathogens but also by potential pathogens in immunological deficiency syndromes has been clearly established (Gatti & Good 1970) In fact most often the infections caused by potential pathogens are fatal in children with combined congenital immune deficiency within the first or second year of life (Cole et al 1969)

The achievement and maintenance of a germfree or gnotobiotic state respectively by the means of complete isolation and decontamination of the endogenous microflora by antibiotics may enable the medical team to attempt promising treatments of the underlying disease such as transplantation of thymus or bone marrow without the threat of complicating infection or pronounced secondary disease (De Koning et al 1969)

With this background of information and after the diagnosis of lymphopenic hypogammaglobulinemia was established in our patients a concept had to be developed in order to control the present infection as well as to initiate prophylactic treatment to inhibit further infections Consequently therapy consisted of two aspects. First strict isolation to exclude the contamination by exogenous microbes Second decontamination of the endogenous microflora containing potential pathogens by means of antibiotic treatment, disinfecting and sterilizing procedures

Prior to reconventionalization, after the planned therapy had been completed the gnotobiotic care included the introduction to

the children of a normal microflora in order to prevent unwanted microbial colonization

Microbiology

During the time of observation sampling was done from different sites regularly twice a week external ear nose oral cavity groin anus back umbilicus axillae toes preputium (until circumcision) urine and feces The isolator and the introduced items were tested microbiologically at irregular intervals gloves locks plastic walls drugs alimentation brushes etc.

The cotton of the swabs were prepared in brain–heart suspension The samples were cultured on the following plates blood agar enterobacteriaceae agar (MacConkey) or endo agar (S 110 staph) Sabouraud dextrose agar Fortner plate and at the same time cultured in brain–heart suspension for 24 to 48 hours Mixed cultures were then fractionated and the single strains typed biochemically

For quantitation of the intestinal microbes a fecal sample of 0 5 g was mixed with 4 5 g brain–heart suspension and diluted serially At the same time the samples were incubated in thioglycolate (for anaerobic culturing) as well as on plates (for aerobic and anaerobic culturing) The anaerobic culturing was done in evacuated anaerobic jars as described by Lerche & Reuter (1960)

The following media were used Endo agar or MacConkey No 3 enterococci confirmatory agar S 110 staph (Chapman) Sabouraud-glucose agar tomato juice agar clostridial reinforced agar and Fortner plate

The bacteria to be given for the implantation of a normal intestinal microflora were received from other laboratories (Bifidobacteria Bacteroides vulg [2]) or from the fecal flo t a healthy donor Of several children tested one three-year-old healthy child was chosen to serve as a donor for the accompanying microflora as well as for the non-obligatory one

The bacterial strains were separated by culturing on plates and stored in liquid nitrogen as well as in a sample of the fecal specimen The inoculated Bifidobacteria were given in milk. The Bacteroides which were cultured in thioglycolate were applied orally suspended in that medium (+ milk) and rectally The aerobic bacteria were given in 0 9% sodium chloride

The sensitivity to antibiotica of each single bacterial strain was tested by agar diffusion test

Isolation

The isolation of the infants took place in plastic isolation systems constructed in analogy to isolators used for the care of germfree animals.[3] Each system consisted of a maintenance and a storage isolator They were made of polyvinylchloride (PVC) and placed on mobile tables of aluminum (Fig. 11) Each isolator had its independent air filter system to provide sterile air The storage isolator had an entry port to which an autoclaved drum could be attached for loading the isolator with sterile items Three neoprene gloves are attached to work inside the isolator The isolator itself was connected to the maintenance isolation system by a plastic tunnel which was 0 7 m long This tunnel could be locked from both sides so that the isolators could be separated and one of them used as transport isolator The living room for the infant was 0 75 m high 0 7 m wide and 1 5 m long during the first year of life and 1 0 m high for the second year of life Five neoprene gloves allowed manipulations within the isolator The outlet port was built by such a device that after being wrapped in a plastic bag used outgoing material was passing a dip tank filled with phenole This germicidal trap enabled the attending personnel to withdraw all items from the isolation very quickly so that blood specimen etc could be obtained without considerable delay of

Courtesy of Dr Schuler Malyoth Starnberg.
C urtesy of Prof Werner Bonn.
I collaboration w th von Stengim Metall u Plastik Radolfzell Germany



Fig 11 Plastic isolation systems Maintaining isolators connected with storage isolators by plastic tunnels At the right side of the picture an autoclaved drum is visible. It is connected to the storage isolator to introduce sterile items.

time Infusions were performed by leading a tubing set through the dip tank. The isolation system for children of the age above 2 years until 5 years consisted of a bed isolator storage isolator and a playground isolator (2 m high 2.5 m wide and 3 m long) Seven neoprene gloves were attached to the playground so that the infant could be held from outside in every position (Fig. 12)

Prior to the placement of the children the isolation systems were sterilized by 2% peracetic acid Peracetic acid sprays were used to introduce the sterilized items uncontaminated into the isolation systems several times a week after the port entry was locked safely from the inside of the isolator An extra tubing system allowed the evacuation of the remaining acetic acid without entering the isolator

All introduced materials were presterilized except certain oral drugs Linen diapers gauze etc were autoclaved Books, toys balls were either sterilized by ethylene oxide or ionizing radiation from a Cobalt 60 source The alimentation was provided by commercially available sterile food or autoclaved food and liquids

Decontamination

Prior to the entry into the isolation system the infants were decontaminated in order to achieve a gnotobiotic state The decontamination procedure was continued during isolation. The following regimen was followed



Fig 12 Playground isolator (left) connect ... he maintenance (middle) and the storage isolato

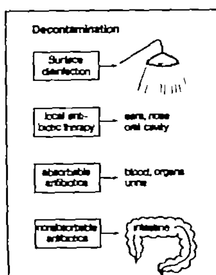


Fig 13 Principle of decontamination.

– Surface disinfecting agents were used to clean the skin Since TEGO[a] compound (C_{12}–H_{25} –NH–C_2H_4–NH–C_2H_4–NH–CH_2–COOH)may cause microtraumatic lesions each cleansing was followed by a bath with sterile water and the application of sterile baby oil

– Antibiotic ointments and sprays were used to treat bacterial contaminations of ears nose, throat and preputium (until circumcision)

– Absorbable antibiotics were given orally to bacteria in places not accessible to ...al treatment. Non-absorbable antibiotics ... fungistatics were given to eliminate intestinal microflora and to prevent fungal overgrowth (Fig. 13)

(a) First stage of decontamination

At the time when the decontamination therapy was initiated both children suffered from pronounced diarrhoea the feces were mixed with mucus and blood At the same time signs of a purulent skin disease of the anal area were apparent At inventory the following microbes could be cultured in both children (Table 3) The treatment of the children in order to ach e e decontamination consisted of the antibioti listed in Table 4

Four weeks after institution of the deconta mination regimen the microbiological cultures showed no microbial growth in either child when different sites were sampled (urine feces nose ext ear throat skin–5 sites including the bath water)

Eight weeks after starting decontamination, E coli interm. from urine and feces of E. R and Aerobacter aerogenes from urine of W R. could be cultured, thus demonstrating the suppression only of the microbial flora but not its complete elimination

In the following months it could clearly be shown that microbial growth was only suppressed by the applied decontamination therapy though the number of microbial strains had been reduced After 8 months of decontamination in E R the following microbes could

Table 3 *Bacteria cultured from various sites of E R and W R before decontamination*

(Anaerobes were not differentiated)

Site	E. R.	W R.
March 28		
Urine	E. coli mucosus Staph. aureus Staph epiderm	E. coli Klebsiella atlantae Enterococci
Feces	E. coli E. coli mucosus Staph. aureus Enterococci	E. coli Klebsiella atlantae Staph. Epiderm. Enterococci
Nose	Sarcina	Sarcina
Ext. ear	Sterile	Staph. epiderm. Staph. aureus
Umbilicus	Staph. aureus Staph. epiderm. Enterobacter aerog.	Staph. epiderm.
Axilla	Staph. epidermidis	Sporeform. bacilli
Groin	Staph. epiderm Staph. aureus E. coli	Staph. epiderm.
Anus	Staph. aureus E. coli	Staph. aureus Staph. epiderm. Enterobacter aerog Klebsiella tlantae
Back	Staph. aureus Staph. epiderm. Sarcina	Sporeform. bacilli
Toes	Staph. epiderm. Sporeform bacilli	Staph. aureus Sporeform bacilli
Preputium	Staph. epiderm. E. intermed.	Not done

Table 4 *Types and dosages of antibiotics used for the first stage of decontamination of E R and W R*

Antibiotic ointment and spray for external ear nose oral cavity and preputium (until circumcision)			
E. R. Neomycin, Bacitracin, Gentamycin sulfate			
W R. Neomycin, Bacitracin, Gentamycin sulfat			
Surface disinfection—daily bath			
E R. TEGO 103S 1%			
W R. TEGO 103S 1%			
Absorbable antibiotics	*Days*	*Daily dose*	*Total dose*
E. R. Ampicillin	50	600–900 mg	33 6 g
Clotrimatole	143	900–1000 mg	124.5 g
W R Ampicillin	33	600–900 mg	.5 g
Nonabsorbable antimicrobial agents		I U	I U
E. R Polymyxin E	33	1–3 Mio	$0 9\times10^{9}$
Neomycin sulfate	33?	1–3 Mio	$0 9\ 10^{9}$
Nystatin	189	0 3–3 0 Mio	$0 28\ 10^{9}$
W R. Polymyxin E	.55	1–4 5 Mio	1.87×10^{9}
Neomycin sulfate	.55	1–4 5 Mio	1.87×10^{9}
Nystatin	264	0 3–2 3 Mio	$0 4\ 10^{9}$

In E. R. nystatin was given for fungistatic therapy During an interval of 143 days this treatment was replaced by clotrimazole

be cultured occasionally Candida albicans Staph epidermidis Enterobacter (trignotophoric state) In W R Klebsiella and Staph. epidermidis could be cultured rarely (dignotophoric state) When microbes could be cultured under antibiotic suppression they were mostly found in throat feces and urine in both children and in the ear of E R. who had an eczema-like skin lesion in the right ear Whereas in W R. Candida albicans was cultured once before entry into the isolation fungi or yeasts have never been cultured afterwards Table 5 shows that marked suppression of the endogenous microflora was achieved but no complete elimination. This is expressed by the percentage of positive cultures of material obtained from various sites

(b) Second stage of decontamination (maintenance)

Antibiotic ointments and sprays for external ear nose and oral cavity and the daily baths with TEGO 103S 1% for surface disinfection were applied as in the first treatment phase

** 783384

Furthermore antibiotics were used as outlined in Table 6

During this regimen of decontamination in both children the number of positive cultures was reduced significantly and further elimination of microbes occurred In E. R Enterobacter could still be found occasionally in urine and feces and Candida very rarely in urine and feces Of 109 samples of urine only 22 were positive for Enterobacter (20%) 24 of 92 fecal samples showed growth of Enterobacter (26%)

In W R only at the plastic wall of his isolator could Staph epidermidis be cultured twice during 15 consecutive weeks This finding can be explained by accidental contamination of the swabs outside the isolation. After achieving zero bacterial growth repeatedly the antibiotic regimen was discontinued whereas the fungistatic nystatin was continued One week after the discontinuation of the antibiotics two sporeforming bacilli B macerans and B polymyxa could be cultured on skin in urine and feces At the same time these spore forming bacilli could be detected in the nystatin compound that was obviously contaminated by the producer The nystatin was

Table 5 *Microbial growth during first stage of decontamination of E. R (upper part) and W R (lower part)*

Site	N	Growth of Bacteria		Fungi	
E R.					
Ear	97	39	40%	30	31%
Nose	97	18	18%	9	9%
Throat	97	52	54%	20	21%
Skin (includ bath water)	485	25	5%	14	3%
Urine	207	79	38%	44	1%
Feces	195	107	55%	9	5%
W R.					
Ear	78	13	16%	0	
Nose	78	8	10%	0	
Throat	78	25	32%	0	
Skin (includ bath water)	390	13	3%	0	
Urine	171	44	26%	0	
Feces	166	78	47%	0	

Table 6 *Types and dosages of antibiotics used during the second stage of decontamination of E. R and W R*

		Days	Daily dose	Total dose
	Absorbable antibiotics			
E. R.	Ampicillin	252	1.5 g	378.0 g
	Dicloxacilli	252	1 0 g	252.0 g
	Clotrimazole	28	1 0 g	28 0 g
W R.	Ampicillin	63	1.8 g	113 4 g
	Dicloxacillin	63	1.2 g	75 6 g
	Nonabsorbable antimicrobial agents			
E. R.	Gentamycin sulfate	462	500– 000 mg	349.5 g
	Nystati	434	3 0–4 0 MioIU	1 64* I U
W R.	Gentamycin sulfate	252	500 mg	126 0 g
	Nystati	83	2.3 MioIU	0.18×10* I.U

then discontinued and no fungal growth was observed thereafter To attempt the elimina tion of the sporeforming bacilli further antibiotic therapy was given consisting of gentamycin sulfate However these bacilli continued to be cultured occasionally during the suppressive therapy In 9 of 77 urine samples (12%) and in 9 of 72 fecal samples (13%) the sporeforming bacilli were found

In E R Candida albicans occurred through out the treatment period After the unsuccess ful attempt to eliminate the Candida by nystatin (0.5–1 5 Mio I U /day) a trial was made *with clotrimazole to improve the unsatisfac* tory results Obviously clotrimazole had no better effects than nystatin Therefore nystatin was increased to 3 0–4 0 Mio I U /day which resulted in a more pronounced suppression of Candida (Table 7)

In both children the purulent skin infec tions and the severe enteritis were successfully controlled by the decontamination therapy During the whole time of isolation and decon-

Table 7 *Growth of candida albicans during different forms of fungistatic therapy in E R*

	Nystati 0.5–1.5 Mio I U /day	Clotrimazol 0 5–1 0 g/day	Nystati 4 0–4 0 Mio I U /day
Urine	37/74 = 50%	13/70 = 65%	7/1 1 = 6%
Feces	9/195 = 5%	3 4 = 1	5/9? = 5%

tamination there was no evidence of bacterial infection. Also there were no clinical signs of infection either by viruses or parasites The gnotobiotic care had to be interrupted for about 20 days in child E R when he suffered a convulsive seizure due to tetanus toxoid stimulation (see above IV) During this interval antibiotic treatment was given parenterally Despite treatment he developed fever and revealed a temporary rise of bacterial growth in the intestines After reinstitution of gnotobiotic care the microflora was again suppressed and henceforth bouts of fever were *not observed*

At the end of the decontamination therapy in both infants a dignotophoric state was achieved though the present microbes were suppressed and could only occasionally be detected by microbiological culturing.

Reconventionalization

It was attempted to restore immunological competence by transplanting fetal thymus in *E R. and maternal bone marrow in W R.* A detailed report about these procedures has been published previously (Flad et al 1971 *a*) During long term maintenance of both chil dren in the isolators it became apparent that their immune responses improved gradually (see V) Therefore after two and a half years of gnotobiotic care reconventionalization was *planned It was decided to reconstitute a nor*

Fig. 14. Stepwise inoculation of bacteria in W. R. during isolation.

mal intestinal flora before termination of isolation in order to control any unforeseen event. To minimize the unknown risks the inoculation of bacteria was performed step by step so that an infection possibly arising from the implanted bacteria could be treated by antibiotics specifically on the basis of the previously known sensitivity tests.

There were 3 steps of inoculation:

step 1: anaerobic bacteria to form a basic flora,

step 2: aerobic bacteria to form an obligatory accompanying flora including nonobligatory bacteria known as non-pathogenic,

step 3: a fecal specimen of a healthy child to implant possibly existing but unknown factors to influence the microbial interaction in the lower intestine.

Two strains of bifidobacteria and subsequently single bacterial strains were inoculated in child W. R. step by step, each after an appropriate interval of observation (Fig. 14). In W. R. there was a dignotophoric state due to the association of the sporeforming bacilli B. macerans and B. polymyxa. Bifidobacteria (Nos. 11 A and 13) were given for one week at the quantity of 1×10^{6} each in 100 ml milk and subsequently in the concentration of 1×10^{10}/100 ml each for two weeks (Fig. 15). After an observation period of five months during which the stable colonization of the bifidobacteria and the varying behaviour of the sporeforming bacilli was followed Bacteroides vulg. (BM 137) was given in thioglycolate in the amount of 2×10^{8} by oral route as well as by rectal implantations (Fig. 16).

Four months after the successful implantation of Bacteroides E. coli were given by oral and rectal instillations of 2×10^{8} bacteria. Two weeks later Strept. fec. was implanted by oral and rectal application of 2×10^{8} bacteria and 2 weeks later followed by the implantation of 2×10^{8} Staph. epiderm. also by oral and rectal application. One week later a fecal specimen of 1.0 g was implanted rectally, obtained from a healthy child (Fig. 17).

The strategy of the association of E. R. with microbes was planned in such a way that combinations of several bacterial strains were given (Fig. 18).

E. R. had also been in a dignotophoric state since a strain of each Enterobacter and Candida albicans was suppressed only by the antibiotic treatment. After the discontinuation of the antibiotics, a fecal specimen of W. R. was implanted, when W. R. had been associated

Fig. 15. Titres of implanted Bifidobacteria and the sporeforming bacilli in W. R. during isolation from September till November 1970.

Fig 16 Titres of implanted Bacteroides Bifidobacteria and spore-forming bacilli in W R during isolation from February through March 1971

Fig 17 Microbial interactions following inoculation of a normal microflora in W R. during isolation

Fig 18 Stepwise inoculation of bacteria in E. R. during isolation

with Bacteroides Bifidobacteria and spore-forming bacilli Two weeks later 2×10^{8} Strept. fec and 2×10^{8} E coli were given rectally followed by the implantation of Staph epiderm

In E. R Candida alb was no longer detected in the feces after an anaerobic and subsequently an aerobic microflora was implanted Furthermore the implantation of Bacteroides Bifidobacteria Strep fec and E coli did not seem to have any adverse or enhancing effects on the number of those microorganisms per g feces that had been instilled previously

Fig 19 Follow-up of the association with a normal microflora of E R. during isolation

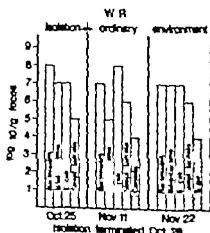


Fig 20 Follow-up of implanted microflora in W R before and after isolation Hatched bars, spontaneously acquired organisms.

Following the inoculation of normal microflora into the intestinal tract both children were still in a gnotophoric state until they were released into the conventional environment

In W R. the intestinal microflora remained stable following the release into the ordinary environment Only occasionally new bacteria could be found such as Candida albicans and Staph. aureus (Fig 20)

In E. R the intestinal microflora was stable for some time following implantation but later on new microorganisms could be found in the feces. E. coli haemolysans Proteus mirabilis Citrobacter Freundii They may have influenced the growth of the other intestinal microbes Some of the variations of bacterial growth which were observed may have been caused at least partially by temporarily applied absorbable antibiotics (Fig 21)

VII PSYCHOLOGICAL OBSERVATIONS OF THE PATIENTS AND PSYCHOTHERAPEUTIC PROBLEMS

General Remarks

The reported situation of raising a pair of twins in plastic isolation provides an exceptional case of environmental deprivation which does not fall into the category of social isolation neglect or total lack of stimulation. The latter has been thoroughly described in experimental animal research by Harlow (1958 1966) and for social deprivation and inadequate stimulation of infants in institutions by Spitz (1945)

Reverse isolation as a relatively new suppor

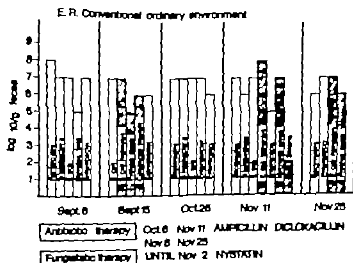


Fig 21 Follow-up of implanted microflora in E. R after the isolation was terminated. Hatched bars spontaneously acquired organisms.

Table 8 *Particularities of psychological situation of the twins during maintenance in plastic isolators*

Characteristics of reverse isolation	Characteristics of psychological situation
1 Relatively unchanging and limited environment	Little possibility for experiencing and imitation
2. Motor restraint	Extreme and prolonged dependency on human objects. Lack of possibility to initiate interaction other than verbally
3 Separation by plastic wall	N direct skin contact
4 Inner world of the isolation versus external environment	Motoric activity restricted to inner world, only sensoric participation in external environment

tive method in the treatment of transient or congenital immune deficiency has previously not been applied to infants for a period of more than 2 1/2 years. Nothing was known about the possible hazards of the restricted environment of a plastic isolation system for the development of behavior patterns and psychic structure

The characteristics of the cases described in report are in several aspects different from those discussed in retrospective studies on social deprivation (Beres & Obers 1950) or criminal neglect (Davis 1940 1946 Koluchowa 197?)

1 Our patients did not suffer from lack of stimulation or grossly inadequate stimulation. They rather grew up in a comparatively monotonous environment offering only selective and limited experience but adequate social stimulation.

2 The twins were exposed to a primarily identical environment They displayed different characteristic of de elopment i e they were differently affli ted by reverse isolation

3 The psycholog al de elopment of the twins was documented during is lati n where-by certain variables of the situation could be changed and the respective effects observed.

The particularities of the psychological situation are given in Table 8

The limited and unchanging evironment made exploration and new experience nearly impossible This lack of a complex stimulating environment promoting spontaneous activity was aggravated by the confinement to a space not much larger than a baby bed. The children could initiate interaction only verbally They were therefore mainly watching the activities of the nurses at a time when toddlers usually follow their mothers and constantly engage in interaction with them The limited amount of everyday experience could affect for instance the formation of practical concepts and impair intellectual development

Table 9 summarizes the psychological situation of the twins with regard to the attending nursing personnel

Four nurses took care of the children around the clock replacing the mother who could not participate in raising the children Different from a family setting there was no role distribution between the members of the nursing team. Each nurse took over complete responsibilities during the time of her shift not only caring for the physical well-being of each child but also applying her specific training objectives in handling the children

The twins were therefore confronted with

Table 9 *Psychological situation during isolation of the twins with regard to the nursing personnel*

Characteristics of nursing situation	Consequent psychological situation of the twins
1 Four nurses, no role distribution	Four equivalent primary object
2 Different educational goals and training objectives	Changing and partly contradictory information
3 Overprotecti e and at the same time restricti behavior patterns	Passiv recepti and dependent position

four equivalent primary objects who displayed different and partly contradictory educational goals and training objectives. The lack of experience in handling this new and demanding mode of treatment contributed to overprotective and at the same time restrictive behavior patterns in the nurses

Handling of infants has often been equated with skin-contact since one is usually not found without the other The importance of skin contact in early infancy which has been stressed frequently refers to the importance of attachment to the infant as shown by frequent handling of the child The twins E. R and W R. displayed normal reactions to handling and being cuddled with the black rubber gloves attached to the sides of the isolators

Methods of Psychological Study

The twins were 14 months of age when psychological evaluation was first initiated

First period 0–14 months retrospective evaluation

Routine clinical records nurses daily shift notes interviews with nurses pediatricians, interns and physiotherapist.

Second period 14–24 months psychological evaluation and therapy

Bühler–Hetzer Development Scale (Bühler & Hetzer 1970· Simonsen 1947) administered every three to five months by a psychologist who was not a member of the treatment team.

Direct observation daily protocols of play therapy (play therapist) group sessions and interviews with the nurses in charge (psychotherapist), weekly meetings of all staff members engaged in the treatment of the twins film protocol of development (16 mm sound-film)

Third period 25–35 months psychological evaluation and therapy

Bühler–Hetzer Development Scale

Direct observation protocols of play-therapy 3 times a week (psychologist) time-sampling of spontaneous behavior once a week (psychologist) group sessions and interviews with the nurses (psychotherapist psychologist) film protocol of development (16-mm sound-film)

Discussion of Methods

Buhler Hetzer Development Scale

The test which covers the ages from 1 month to 6 years is commonly used for the first 2 to 3 years of life The test-scores calculated give an estimation of developmental progress The child s reactions are evoked in a standardized situation The test values achieved on different *subscales of the test allow comparison with* the norms of the appropriate age group An overall developmental quotient is calculated from the six subscales of the test

sensory perception	SP
body control	BC
social contact	SC
learning ability	LA
handling of material	HM
intellectual capacity	IC

Time sampling: all spontaneous behavior that was displayed within an hour was dictated on tape in two-minute sequences.

This method allows an estimation of the amount of time spent engaged in certain activities (e g. rocking) and of the diversity of activities displayed by the child

Group sessions (see chapter VIII)· Psychological observations of the nursing personnel

Following the first psychological evaluation psychomotor development was promoted by intensive play therapy and physical therapy

Findings

A Behavior patterns during first period (0–14 months)

E R Feeding: recurrent vomiting persisted throughout the first year

Sleep his sleep was easily disturbed even at night. He regularly woke up when the nurses were busy at the storage isolator at night. When roused from sleep he was at once wide awake

falling asleep and waking up occurred without transition stage of drowsiness or somnolence

Interaction E. R was reported as a passive friendly child. He was extremely fond of being handled and caressed sometimes beginning to cry when the nurse ceased to caress him

Habits occasional jactation of the head From the time of the convulsion subsequent to tetanus toxoid frequent grimacing. These symptoms together with the retarded development, gave rise to the suggestion of a possible brain-damage as a consequence of the seizure

W R Feeding recurrent vomiting in the first months later on no feeding problems.

Sleep slept well difficult to wake up extended transition stage of half an hour before being wide awake when roused from sleep

Interaction eager to initiate interaction tried continuously and successfully to attract the adults attention by calling or shaking of cot, nurses favorite

Habits W R. developed the habit of rhythmic rocking while sitting or standing towards the end of the first year

B Psychological evaluation during second period (14–24 months)

1 Observation of behaviour at 14 months of ... The extremely vivid and intensive eye ...act—being at the same time besides verbal utterances the only object-directed activity not hindered by the plastic wall—was the children s most striking characteristic at the time of the first psychological evaluation

E. R impressed as a delicate child, friendly and passive His movements were slow and unsteady he gave the impression of weakness when handling play material He could not sit unaided for some time

W R was described as healthy looking and vivid. He successfully tried to catch attention by calling one of the two words he had acquired He was vigorously participating in interactions with nurses and strangers alike shaking with eagerness to imitate play

2. Sensory-motor intelligence When first

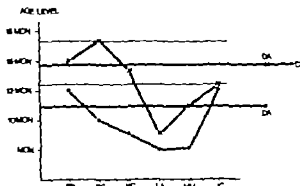


Fig 22 Bühler–Hetzer developmental scale at age 14 months W R. x—x E R. ●—● Mon = months CA = chronological age DA = developmental age SP = sensory perception BC = body control SC = social contact LA = learning ability HM = handling of material IC = intellectual capacity

tested with the Bühler–Hetzer Development Scale at 14 months of age (Fig. 22) both twins demonstrated impaired ability to handle play material (subscale HM) and inferior learning ability and memory (subscale LA) Both test profiles were unbalanced still *W R* s developmental quotient of 100 corresponds to the mean of his age group while *E R* shows a developmental delay with a developmental quotient of 80 His developmental age (DA) is below his chronological age (CA) and below the lower margin of the normal range for his age group

Interpretation of the retardation in subscale HM The lack of skill in handling play-objects at this age was due to an almost complete absence of toys available to the twins. As for LA and memory the following hypotheses were put forth at the time of the first evaluation

(a) The objects used to test these abilities were new to the children and therefore not meaningful

(b) It was most striking that both children were intensively and constantly watching the face of the testing psychologist rather than concentrating on the play material offered thereby possibly missing the meaning of the simple instructions given to them

In the following months additional play ob-

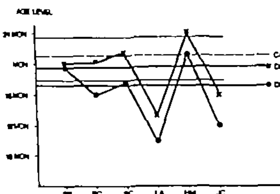


Fig 23 Bühler–Hetzer developmental scale at age 19 months, W R., x—x, E. R. ●—● For abbreviations see Fig. --

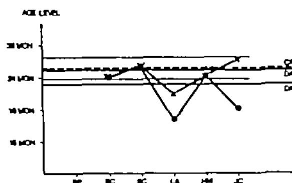


Fig 25 Bühler–Hetzer developmental scale at age 27 months W R. x—x E. R. ●—● For abbreviations see Fig. 22.

jects were provided and intensive play therapy was introduced

Five months later at 19 months of age (Fig 23) the developmental quotient of both children had remained the same The ability to handle play material (HM) was improved as a consequence of the intensive training with the play therapist

Learning ability (LA) remained below average Intellectual capacity (IC) had dropped to a lower value in both children neither one could solve the simple problems first introduced for this age group

Five months later at 24 months of age (Fig. 24) still no improvement in these subscales of the test was noticed.

Effective problem-solving behavior was first realized in W R. at 27 months of age (Fig. 25 IC) two months after he had been transferred to a larger isolator to which a third cubicle serving as a playground had been attached E. R. who remained in the small isolator showed no comparable improvement.

At 2 years and 7 months both test-profiles were more balanced (Fig. 26) This test was given after play therapy had been changed from a systematic training of isolated functions such as hand-eye coordination recognition of pictures naming of objects, differentiation between colours to an analytically oriented one with the aim of eliciting spontaneous activity and promoting the development of ego autonomy

Interpretation of Psychological Findings

In the comparatively monotonous environment adaptation to new situations was seldom necessary Play activities once learned showed little variability and a strong resistance to

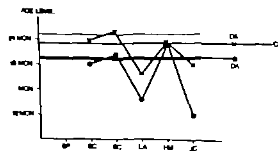


Fig 24 Bühler–Hetzer developmental scale at age 24 months. W R., x—x, E. R., ●—● For abbreviations see Fig. 22.

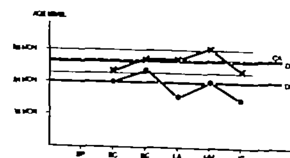


Fig 26 Bühler–Hetzer developmental scale at age 2 yrs., 7 months. W R., x—x, E. R. ●—● For abbreviations see Fig. 22.

change The restricted environment allowing very little exploratory behavior led to an almost complete lack of spontaneous activity except for inducing the adults to put on the isolator gloves Apparently the crucial factor leading to the formation of practical concepts seems to be a certain amount of everyday experience. Infants are usually exposed to a wide range of new situations every day This encounter stimulates the development of a differentiated spectrum of sensory motor intelligence A formal and repetitive exposure to one form of a new concept the enforced promotion of isolated functions—as was aimed at in play therapy—does not seem to make a great deal of difference and is also extremely timeconsuming and little rewarding for both the child and the play therapist.

The construction of an isolator which imitates normal environment appeared to be impossible The predominant problem therefore was to help the children overcome the position of dependent passivity Stimulating material was limited it had to be used inventively and imaginatively in many ways and for different purposes—a task not easily accomplished by a two-year-old who is just learning that definite objects have definite names and can be used for definite manipulations

In this situation the main problem was the on of spontaneous activity necessitat _ at the same time a change in the stabilized interaction patterns of nurses and children which actually promoted passivity A change in play therapy to an analytically oriented one was difficult to carry out, since the nurses tended to take over—helping the children by telling them what to do—whenever the psychologist tried to induce a situation where self-directed activity was called for Both children reacted to such less defined unacquainted situations with displaying signs of intense uneasiness uncertainty and withdrawal

Certain aspects of the psychological development of E. R and W R ought to be discussed in more detail

Object relations

Attachment behavior as a sign of the child s emotional tie to his mother has been described by Bowlby (1969) Attachment behavior such as calling smiling watching turning to the approaching nurse when engaged in play with a stranger was displayed by both children. Whether the ability to differentiate between mother substitute and stranger was acquired later than normal (Achtmonatsangst Spitz 1965) cannot be decided retrospectively

Attachment behavior and object constancy (Gerwitz, 1961 Piaget 1955 Schaffer 1963) i e the concept of the object as having an existence which continues outside one s perception of it—were already firmly established at 14 months of age

Until 2 years of age neither child showed a detectable preference for one of the nurses The question whether the black rubber gloves attached to the sides of the isolators were experienced as part of the attending adults and complicated the differentiation between the four nurses at an early age is open to discussion. At 2 years of age W R. definitely preferred one of the nurses and learned to call her by name Clinging (Bowlby 1969) could not be observed due to the separating plastic walls Neither child moved into the direction of the mother substitute for comfort or to be consoled. Clinging therefore was not only actually absent but the inherent turning to the mother figure for help and comfort was absent as well This might very well have to do with the lack of physical contact and the confinement to the isolators where the nurses were only close during the usual handling of the children while dressing and feeding them and in the spare time for play Naturally they could not be followed when they turned away

Following—another typical attachment behavior of the small child—was therefore impossible but was seen rudimentary since the children usually stayed in the corner of the isolator closest to the nurse W R. later followed the nurse in his large play-isolator

Reactions to separation (the nurse turning

to the other twin or leaving the room) were signs of sadness and retreat in W R who for instance sucked his thumb under these circumstances, while E. R. habitually fell into rhythmic rocking movements.

At the time W R. began to prefer one of the nurses he showed separation anxiety—crying calling her name—for a few weeks

Ego development

Extreme dependency kept the children for an unduly long period of time in a completely receptive position.

Play activities. Until one and a half years of age both children mainly wat hed the attending adults or tried to induce them to put on the gloves. Reality seemed to exist mainly outside the isolator Later on W R. seldom engaged in spontaneous play activities when unattended He almost exclusively used toys when playing and repeated operations and games used in play therapy

E. R. showed more ingenuity when playing alone He mostly used other material—like bottles and diapers—when playing, preferring repetitive movements

Comparing the twins when playing alone W R.s play activities were less ingenious and rhythmic but more directed towards objects and achievement He needed constant approval. E. R.s play gave the impression of kinaesthetic self-stimulation was ingenious and rhythmic though repetitive

Tolerance of frustration The lack of possibility to try out and choose alternatives led to a comparatively narrow spectrum of different activities and reaction patterns and consequently to a low frustration tolerance The prohibition of an activity—e g. throwing of toys into the dip-tank—was usually followed by retreat and not by alternative behavior releasing some of the tension and excitement inherent in the former activity

W R. s reactions again were age-adequate forms of retreat e g. sucking of thumb showing of belly E R displayed intensive rhythmic scratching with both hands reversal of affect such as sudden laughing or motionlessness up to three minutes followed by sudden waking up In such instances breathing was pronounced

One of the most frustrating experiences was the collection of urine a procedure during which the twins had to be tied to their beds lying on their back for periods up to several days.

W R. acted hurt in such instances he would not look at the nurse would cry softly or sleep for several hours at a time when he usually was awake Under these circumstances E R. was restless rolling his head back and forth screaming whenever someone came close to the isolator He was constantly trying to free his hands or legs being in a perturbed emotional state

Development of the will. When the twins were 2 years old negative and obstinate behavior which was predominantly oral rejective and centered around the eating ritual first gave rise to educational problems. It seemed difficult to learn to propose alternatives, the rejecting negative phase was prolonged The limited environment must be held responsible for the inflexibility of behavior patterns since W R. greatly improved and began try out provoking alternatives when transferred to the larger play isolator at 26 months of age. Manipulation of the distance to human objects and moving out of reach were the precursors of greater flexibility of behavior patterns

Anxiety and fear Both twins showed anticipating fear of medical procedures such as venepunctures and tried to protect the location on their body that had been hurt previously Both cried when accidentally left in the dark (usually a nurse was present at night and a dim light was on)

W R developed separation anxiety at 2 years of age He acted afraid when confronted with a new situation e g. when a swing was installed in the playground isolator

Habit training Habit training was initiated when the twins were two years old The anal phase was fully developed in W R. Mo t

change. The restricted environment allowing very little exploratory behavior led to an almost complete lack of spontaneous activity except for inducing the adults to put on the isolator gloves Apparently the crucial factor leading to the formation of practical concepts seems to be a certain amount of everyday experience Infants are usually exposed to a wide range of new situations every day This encounter stimulates the development of a differentiated spectrum of sensory motor intelligence A formal and repetitive exposure to one form of a new concept the enforced promotion of isolated functions—as was aimed at in play therapy—does not seem to make a great deal of difference and is also extremely timeconsuming and little rewarding for both the child and the play therapist.

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Reactions to separation (the nurse turning

Table 10 Synopsis of psychosomatic symptoms of E. R. and the patient's disposition at the time of their first occurrence

Age at time of observation	Localisation	Somatic disposition	Psychosomatic reaction pattern
(months) ca. 1	Skin	In isolation E. R. was never completely freed of a fungus located on the skin and in his ear. Itching	Frequent scratching, often rhythmically using both hand simultaneously. Predominant situations eliciting scratching: when left alone in the sequence: rocking-scratching when scolded (retreat) when challenged with definite pressure (eating, toilet training)
29	Skin, arms and back	Development of probably allergic exanthema on the day of release from isolation lasting three days. Excessive perspiration	Scratching as above
4	Respiratory tract, lungs	Later (at the day of release from isolation) auscultatory verification of "asthmatoid breathing"	Pronounced breathing, i.e. forced inspiration and exspiration followed by a prolonged pause when scolded
4			Inarticulate vocalisation expelled with vigorous pressure (tape-recordings)
30	Respiratory tract	First cold and bronchitis	Having overcome the bronchitis, he retained by the habit of pronounced breathing eventually coughing and finally vomiting when on [illegible]
33	Respiratory tract	Recurrent bronchitis	First severe attack of asthma when first separated from the nurses three months after release from isolation

Consequently frequent misunderstandings arose which increased the probability of extinction of fragmentary or whole behavioral sequences. In turn this may have added to the delay of a meaningful behavior in E. R. Being handicapped as E. R. was whether as a consequence of the seizure (s. Clinical Course) or of an early disturbance in nurse-child interaction (or a combination of these factors) his needs were qualitatively different from those of his brother. He therefore was more severely handicapped by isolation. Despite all psychotherapeutic efforts it may have aggravated his retardation in psychomotor development.

Symptoms with possible psychosomatic background

Diarrhoea was seen regulary in both children as a reaction to the stress of the urine collection procedures. In addition E. R. frequently vomited the first meal fed to him after having been untied. Both children simultaneously developed diarrhoea a few days after separation from each other following E. R.'s release from isolation. At about one and a half years of age E. R. once had a convulsion like seizure when the feeding order was changed and he was fed last for the first time. Three months after release from isolation E. R. developed asthma. Table 10 gives a list of psychosomatic peculiarities displayed by E. R. together with the first time of their occurrence and the child's somatic disposition at the same time.

Release from Isolation and Beginning Adaptation to a Normal Environment

At the time of release from isolation in August 1971 E. R. had lived 29 months in a plast

Conflicts between the team and others

Participation in a project much discussed in public exposed the members of the team to envy and criticism by other hospital personnel The nurses themselves were afraid that their highly specialized task would leave them without the necessary training and practice in general patient care and preclude later occupational progress

Emancipation of the nurses from the pattern of the dependent and subordinate paediatric nurse proceeded parallel with the development of the will in the twins This influence on ego development of the nurses furthered by projective identification was an interesting phenomenon observed in the course of treatment of the twins during isolation

X DISCUSSION

Immunological Aspects

The diagnosis in these infants is consistent with an immunodeficiency syndrome with impaired cell mediated and humoral immunity The syndrome cannot be classified in the categories which have been termed recently (Fudenberg et al 1971) Rather this syndrome belongs to the various forms of unclassified diseases which need further evaluation and classification

The major problem to be discussed is the question as to which extent immunological parameters may be altered by the maintenance in a gnotobiotic environment.

First with regard to *humoral immunity* it is known from experiments with germfree mice that the postnatal increase of immunological competence to the antigen sheep red blood cells is identical in germfree and conventional mice (Bosma et al. 1967) The finding that the kinetics and the number of plaque forming cells are not different in sublethally irradiated germfree and conventional mice has been taken as evidence that the differentiation of antigen-sensitive cells from more primitive elements in the bone marrow and thymus is the same in germfree and conventional mice (Shearer et al 1969) Low levels of gamma-globulins and the relative lack of morphological signs of immune responsiveness in germfree mice (Gustafsson et al 1959) do not imply an underdeveloped immune capacity but rather the absence of immunologic expression due to antigenic stimuli

Second with regard to cell mediated immunity it has been recently reported that germfree rats although having only 20–50% of the lymphoid tissue of conventional rats reject allogeneic skin grafts faster than conventional animals (McDonald et al 1971) Furthermore lymphocytes of germfree rats reacted earlier and more vigorously in mixed lymphocyte cultures than lymphocytes of conventional rats (McDonald et al 1971) This finding has been explained on the basis of a larger pool of immunologically uncommitted cells in germfree compared with conventional mice

Third non-specific defense mechanisms e g the phagocytic potential of cells of germfree mice is not different from that of conventional mice (Perkins et al 1966)

Taken together these findings in germfree animals strongly suggest that the ontogeny of immunological precursor and effector cells is an intrinsic property of the organism which seems to be independent of the antigenic input.

In this context the finding of low levels of immunoglobulins and the lack of isohaemagglutinins in these twins if somehow induced by the gnotobiotic environment would only reflect *a lack of expression of humoral immunity* and not a lack of immune competence. The fact that sensitization and antibody formation to bacterial and viral antigen could hardly be elicited in these children underlines the primary immune deficiency involving B-cell com-

petence. The delayed rejection of allogeneic skin grafts and the lack of sensitization to DNCB indicates a deficiency of the T-cell system. Whether the response of lymphocytes to PHA is under gnotobiotic conditions, a reliable parameter of cell-mediated immunity is at present a matter of discussion. There is some evidence in germfree mice which indicates that their lymphocytes respond less to PHA than those of conventional mice (van der Waaij 1971). This could mean that cross-reacting bacterial antigens could play a role in the PHA-induced response of lymphocytes.

The stepwise reconventionalization of the children by implantation of a controlled microflora (see VI) resulted in a rise of serum immunoglobulins.

Also the isohaemagglutinin titres became positive. Later in a normal environment both children developed severe bacterial and viral infections (to be published). Clearly a restoration of immune capacity was not achieved by the various therapeutic attempts and an evidence for a complete immunological maturation during 2 1/2 years of gnotobiotic care was not obtained. We think, however that maintenance in a gnotobiotic state of infants with primary combined immunodeficiencies is necessary as supportive treatment until a restoration of immune capacity is achieved by bone marrow transplantation or other means. In certain instances, however a delayed yet spontaneous development of the immune system may be considered.

Gnotobiotic Aspects

The treatment of congenital combined immunodeficiency syndromes which usually are fatal seems to be possible since Gatti & Good (1970) Meuwissen et al. (1971) De Koning et al. (1969) Bach et al. (1968), and August et al. (1970) reported about successful reconstitution of immune competence in various immunological deficiencies by bone marrow and thymus transplantations. Many other attempts to graft bone marrow have been performed but most of them without success since in these cases most often fatal infections occurred within short time after the therapeutic trial. These results were reviewed on the basis of own experiences by Meuwissen et al. (1971). Human bone marrow transplants have been summarized comprehensively by Bortin (1970).

De Koning et al. (1969) performed the successful treatment of a patient with Swiss type agammaglobulinemia (severe combined immune deficiency syndrome) under supportive therapy of a laminar air flow cabinet, using germfree techniques. In animal experiments it has been shown that obvious secondary disease did not occur in germfree mice. Microscopic examinations, however of the lymphatic tissues also demonstrated graft versus host reactions (Jones et al. 1971). Whereas death occurred in 100% of the conventional mice after bone marrow transplants, the germfree mice showed a very high survival rate. Decontaminated mice in which bone marrow transplants had been done also survived in a high percentage (Heit et al. 1972). In decontaminated mice a high survival rate could be maintained after bone marrow transplantation and subsequent reconventionalization was performed (Van der Waaij 1971). Thus it seems to be possible to inhibit the complications of secondary disease and to prevent life-threatening infections by the means of gnotobiotic care that are already in use in clinical medicine for the treatment of leukemia and other states of bone marrow deficiency.

The isolation techniques which have been described in more detail elsewhere (Dietrich et al. 1972) have been proved satisfactory for the purpose of prevention of contamination for more than two and a half years of use. Two sources of possible contamination had not been eliminated (*a*) oral drugs or other drugs contaminated by the producer and (*b*) possibly necessary transfusions of blood or blood contents that are associated with microorganisms in case of a bacteraemia (viraemia, fungaemia) of the donor or in case of the contamination by processing of the transfused blood, i.e. to obtain platelets (Buchholz et al., 1971). On

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itivity test of each microbe to be given was known in advance so that each infectious complication could be handled immediately by effective antibiotics The composition of the microflora to be implanted was derived from the knowledge of the ordinary microflora in the intestinal tract of adults and infants respectively (Bendig et al 1968 *a b* Braun et al 1967 Byrant 1970 Donaldson 1964 Gall 1970 Haenel 1965 1970 Hoffmann 1966 Mata et al 1969 Werner 1967) In these publications there is agreement about the obligatory basic flora of anaerobic bifidobacteria and bacteroides Haenel (1965) had shown that enterococci E. coli and aerobic lactobacilli are found constantly in the fecal flora of infants and young adults Besides this accompanying flora there are other nonobligatory microbes as proteus clostridia yeasts, staphylococci and anaerobic sporeforming bacilli This more or less stable composition of the fecal microflora is only significantly altered when antibiotics are given especially for prophylactic purpose thus turning the accompanying flora of E coli enterococci or the nonobligatory flora of proteus yeasts etc. into the main flora (Finegold 1970 Haenel 1965) It also can happen by intense antibiotic therapy that so-called transitory microbes as pseudomonas species may be colonized and may overgrow in the intestinal tract (Noble & White 1969) Such colonization of nonobligatory or transitory microbes may happen when a competitive flora (Stewart 1968) is absent. It was therefore felt that the composition of a normal microflora in the intestinal tract of the children, after being reconventionalized should be able to compete with transitory organisms and thus protect against infections by potential pathogens In addition to the main flora of anaerobes and the obligatory aerobic bacteria E coli and strep faecalis, staph epidermidis were chosen because they are occasionally detected in the feces but definitely in the skin flora of healthy individuals (Marples, 1969 Somerville 1969) The inoculation of the single bacteria step by step showed successful colonization whether given each alone or 2–4 species in combination orally (bifidobacteria) orally and rectally or rectally alone At the end of the association the fecal specimen given rectally of the same child of whom the microbes have been taken did not show any effect to the other microbes This was done in order to find out if there were other factors than the detected microbes to influence the composition of the microflora. One microbial interaction could be seen by observation of the bacterial counts in the feces after the inoculation of staph epiderm the sporeforming bacilli (b macerans b polymyxa) disappeared and could not be detected any more for several months afterwards

It can be assumed that another microbial interaction took place when Candida alb was no longer cultured from the fecal specimen of E. R Though the nystatin treatment was continued for some time probably other factors than fungistatic suppression alone effected the disappearance of Candida since it could not be detected after the discontinuation of the fungistatic regimen. There were no signs of microbial interaction caused by the inoculated strain of E coli alone, a germ which is believed to be very active in this regard Host microbial relationships are difficult to evaluate in human beings. In fact only under gnotobiotic conditions conclusions may be drawn from microbiological and physiological investigations Only few data are available from animal or in vitro experiments (Heniges 1970 Luckey 1970 Schaedler et al 1965 Tanami 1959) These data suggest a large variety of specific effects of microbes on the host s physiology (Gordon & Pesti 1971) But perhaps none of these findings may be of significance for the human situation because they are achieved in different species under different alimentation and, most important, in ex-germfree gnotophoric animals They may be true only in ex germfree but not in decontaminated exconventional animals. To our knowledge no experiments have been done in this regard However observed changes of body weight

WBC Hb survival and cecum weight in mono- and dignotobiotic experiments may indicate the possibility of such interaction also in human patients. So far significant alterations could not be seen in the described children which could be attributed to the gnotophoric states One may assume that possibly existing factors governing the intestinal microecology have not been damaged by the longterm application of antibiotics since the inoculated bacteria have been colonized in the intestinal tract of both children promptly The stabilized gut flora could be observed for some months after the release to the ordinary environment in both children The microbiological survey of the oral microflora showed rapid changes of bacteria towards those that are usually found in the oral cavity

Psychological Aspects

Long-term isolation of the twins led to a learning disorder and to impairment of intellectual capacity as demonstrated by the Bühler–Hetzer Development Scale. This disorder is a consequence of the lack of experience and the relatively unchanging environment, impeding the development of self-directed activity and imitation

Such learning disorders—no capacity to differentiate between relevant and irrelevant stimuli and the absence of generalisation of gained abilities—are described as a consequence of early and long term isolation in experimental animal research (Bernstein 1971 Hymovitch 1952)

The impairment of learning ability however seemed to have been overdetermined in the situation of the twins As its major causes the following possibilities can be listed.

(a) lack of material (play objects)

(b) no spontaneous generalisation of trained abilities (monotonous environment)

(c) passivity no problem-solving behavior (dependent position)

(d) no intentionality (overprotective handling of the children by the nurses)

(e) subject and object not sufficiently separated (no possibility for manipulation at a distance to the objects in the small isolator)

Both children developed the psychopathological symptom of rhythmic rocking In E R it resembled those signs which are described in hospitalism In spite of the frequency and severity of his rocking retreat and autoerotism was only one component in the autistic like behavior pattern Other components in the behavior disturbance were communicative demonstrating the wish for contact Contact in turn caused interruption of rocking.

When motor restraint was no longer severe (W R.—play isolator Fig 12) or after release from isolation (E. R.) both children gave up rhythmic rocking within a few days. The interpretation of motoric symptoms as isolator specific seems to be correct because of the absence of other psychopathological symptoms and disappearance after social contact was well established

The twins were differently afflicted by isolation and the clinical setting where four nurses took over the role of the primary object constituting four interchangeable primary objects

Whereas both children demonstrated a similar and specific intellectual impairment on different levels of overall development interaction with and attachment to the primary objects was different in quality Throughout the treatment period the first born and smaller twin E R remained in the position of the weaker twin (Burlingham 1952) In comparison with his brother W R. he was less articulate (impaired language development) and displayed a stronger tendency to psychosomatic reactions (diarrhoea, vomiting asthma after release from isolation) He displayed a stronger need for physical contact was more sensitive to tactile stimuli and less able to modulate impulse or defer discharge of drive energy The latter contributed to his apparent irritability and restlessness which in turn influenced his ability to concentrate upon an activity

Although close and extended observations were only available during the second and beginning of the third year of life (time sampling) the differences as described above could be interpreted as individual characteristics (Escalona 1965) We assumed that they represented the original differences between the twins in stimulus threshold motor activity sensitivity to tactile stimulation disposition to generalized excitement reactions and participation of organ function in excitation discharge

The modulating role of specific factors during various treatment situations and the influence of the second-twin position however cannot clearly be separated and ought to be considered as well

Disturbances in early mother-child interaction—lack of attachment on the side of the mother and craving for closeness and physical comfort and need for skin contact by the child—have been described and anamnestically verified as typical early constellations found in asthmatic children and adults (de Boor 1965) The combination of disposition and environmental factors may lead to an exacerbation of the disease Environmental conditions specific to reverse isolation such as separation by a plastic wall no close physical contact etc might have been especially prone to contribute to the development of asthmatic symptoms which occurred in E R

Special problems arise when play therapy succeeds in furthering the formation of psychic structure Essentially psychic structure—in the sense of a construct referring to an inner psychic apparatus regulating the mastering of reality and reconciliation of extrinsic demands with intrinsic needs—is formed during the first year of life (Beres & Obers 1950 Freedman & Brown 1968 Freedman 197?)

Relative lack of autonomy which ordinarily is achieved by a child in the anal phase and impaired intellectual operations during this time led to a more pronounced confrontation with the limitations inherent to isolation The children particularly W R. realized these and began to suffer from frustrating experiences (see VIII)

Play therapy implicitly prepares a child for the confrontation with reality In the twins it aimed at the time after isolation Normal ego development manifests itself by the achievement of relative autonomy around the age of two and a half years From this point of view the twins approached a critical age before release By prolonging isolation further this newly achieved autonomy could have led to an inability to cope with the restrictions of isolation Maladaptation and finally regression to a state of early dependency and passivity could have resulted We therefore feel that the twins when released from isolation were approaching a favourable stage of their psychological development

XI SUMMARY

This report describes the clinical immunological and psychological course of non-identical twins with primary combined immune deficiency (type unclassified) during two and a half years of maintenance in a gnotobiotic state.

The germfree techniques used and the antibiotic regimen resulted in a gnotophoric state In one of the twins a germfree state was temporarily achieved

During maintenance in a gnotobiotic state delayed skin reactivity PHA responsiveness of lymphocytes in vitro antibody production to bacterial and viral antigens and immunoglobulin levels were followed Transplantations of maternal bone marrow and foetal thymus did only temporarily improve some of the immune parameters Immunoglobulin levels and isohaemagglutinins remained low and negative respectively which may have been

effect of the maintenance in a gnotobiotic condition

The physical development of the twins was satisfactory although one of them always remained below the 3rd percentile in height and weight

The reconventionalization concept was successful in the association of both children with a normal microflora that was stable also after the termination of the isolation.

The long-term isolation of the twins led to a learning disorder and impairment of intellectual capacity as demonstrated by the Bühler–Hetzer Development Scale This disorder was the consequence of the lack of experience and probably due to the relatively unchanging environment where self-directed activity and imitation could not develop spontaneously Following the release from isolation it diminished rapidly

From the psychotherapeutic point of view the promotion of isolated psychological function by repetitive exposure to circumscribed tasks did not compensate such disorder The promotion of ego autonomy by an analytically oriented play therapy appeared essential

In the absence of other symptoms the development of psychopathological signs involving motor activity such as rhythmic rocking appeared to be isolator specific. They disappeared after release from the plastic tents As their possible cause severe motor restraint should be considered

The gnotobiotic isolation and care as described may be recommended in infants suffering from combined immunodeficiencies It proved a life-saving therapeutic management for the first years of life and a supportive treatment during transplantations of bone marrow and other organs

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ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 241 1973

HAPTOGLOBIN LEVELS IN THE PLASMA OF NEWBORN INFANTS

with special reference to infections

BY TOIVO T SALMI

ALMQVIST & WIKSELL PERIODICAL COMPANY

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with special reference to infections

BY TOIVO T SALMI

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM SWEDEN

ACTA PAEDIATRICA SCANDINAVICA

SUPPLEMENT 41 1973

From the Department of Paediatrics (Head: Professor Tuomas Peltonen, M.D.)
University of Turku, Turku, Finland
and
the Department of Clinical Chemistry (Head: Docent Bernt Laurent, M.D.)
University Hospital, Turku, Finland

HAPTOGLOBIN LEVELS IN THE PLASMA OF NEWBORN INFANTS

with special reference to infections

BY

TOIVO T. SALMI

HAPTOGLOBIN LEVELS IN THE PLASMA OF NEWBORN INFANTS

with special reference to infections

TO THE MEMORY OF MY FATHER

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CONTENTS

INTRODUCTION

Haptoglobin is a plasma protein synthesized by the liver. Its electrophoretic mobility lies in the range of the $alpha_2$ proteins, of which it is quantitatively the most important part. It is a glycoprotein whose carbohydrate content is about 18.5 per cent. Haptoglobin is found in several genetic forms, many of which are polymers of the same basic substance (18).

It has been shown that the biological function of haptoglobin is associated with the metabolic pathways of hemoglobin. Haptoglobin immediately binds the hemoglobin which is liberated when the erythrocytes are broken down. It further transports hemoglobin to the reticuloendothelial system for break down (87, 163). However, haptoglobin itself does not have a decisive role in the metabolism of hemoglobin, because even if haptoglobin is absent there is no serious disturbance in the catabolism of hemoglobin. This is because there are other carrier proteins which are able to transport hemoglobin components, e.g. hemopexin and albumin.

Another important part of the biological function of haptoglobin seems to be associated with acute phase reaction caused by inflammation or some other cell destruction. In connection with infection, trauma or other cell destruction, the concentrations of certain plasma proteins increase. One of these acute phase reactants is haptoglobin. The function of acute phase reactants in inflammatory reactions is largely unknown. There is a theory, however, that these proteins are transport and detoxication proteins. Their function may be to eliminate the products formed by an inflammation process (77).

Various parameters of haptoglobin during the neonatal period differ from that of other age groups. When the erythrocytes with fetal hemoglobin are destroyed, haptoglobin transports the hemoglobin out of the circulation (199). The liver of a newborn infant has not developed to its full capacity of enzyme functions or protein synthesis. In the healthy newborn infants the plasma concentration of haptoglobin is low compared with that of adults (e.g. 13, 133).

An adult organism reacts to inflammation, independent of the cause, with acute phase reactants. These are fibrinogen, haptoglobin, ceruloplasmin, orosomucoid and C-reactive protein. The quantitative determination of these proteins is used to show the acute phase reaction (170). Many protein concentration variations and indirect indicators, for example the erythrocyte sedimentation rate, is also generally used for this purpose. The situation in the newborn organism is considerably different from that in the mature organism. The rate of protein synthesis is lower than in adults (147). Due to the high erythrocyte count, the erythrocyte sedimentation rate, for example, is not reliable for clinical diagnosis in the neonatal period. However, early diagnosis of neonatal infections is most important for successful treatment; therefore a quick method of quantification of an acute phase protein suitable for clinical diagnosis, is greatly needed. One possibility is the determination of plasma haptoglobin concentrations. This can also be used to determine the severity of hemolysis. The investigation of plasma haptoglobin concentrations may, in addition, throw light upon the acute phase reaction itself in this age group.

II REVIEW OF LITERATURE

A REACTIONS OF THE ORGANISM TO INFECTIONS

a. Adult Organism and Infections

The invasion of the organism by an infection triggers a defence system for eliminating the cause of the infection The defence system can be divided into two parts, primary and secondary or local and systemic (171) In the following pages only those defence mechanisms most important to the diagnosis of infections are presented.

Phagocytosis Irrespective of the nature and source of the infecting agent certain changes in the quality and number of phagocytic cells of the blood and tissues always take place In most bacterial infections the organism tends to increase the amount of granulocytes and accelerate their ytic activity In viral infections the amount of granulocytes does not often increase and in some cases it even decreases. In diagnosis of infections the increase of white blood cells and changes in relative amounts of cells of different stages of maturity can be employed (147)

Fever The normal defence reaction of the organism to infections also includes the rise of body temperature. This reaction perhaps inhibits the proliferation of certain microbes (17) Even though fever is not a specific reaction to infections it is one of the most common symptoms

Immunological Reaction Bacteria, viruses and fungi are good immunogens and thus they can initiate the immunological reaction with specific antibodies. The body produces humoral antibodies, which are immunoglobulins and lymphoid cells which are specifically able to eliminate microorganisms Antibodies also have an essential role in specific clinical diagnosis of infectious diseases. Identification of antibodies facilitates specific diagnosis even if the infective agent cannot be isolated

Acute Phase Reaction. When there is an inflammation in the organism caused by an infection trauma, necrosis malignant tumor etc. certain changes take place which taken together are called the acute phase reaction The body usually in the liver increases the production of some proteins: fibrinogen, haptoglobin, ceruloplasmin orosomucoid and C-reactive protein and perhaps others (170) The synthesis of each of the acute phase proteins begins and reaches a peak at different times (30) When these proteins are investigated in an experimental acute phase reaction, for example in connection with an operation it has been observed that the synthesis of C-reactive protein is the quickest and ceruloplasmin the slowest fraction (170) However the syntheses of all acute phase proteins have begun some hours after the stimulus and significantly increased values can be seen as early as during the first 24 hours The changes in immunological reactions are markedly slower they can be seen only after some days (140) The biological role of the acute phase proteins is still obscure The theory that they transport abnormal metabolic products and thus belong to the detoxication system seems clini

cally appropriate but no evidence of this has been presented (77)

The changes in the concentrations of the acute phase proteins and of other parameters monitored in the laboratory can be used in the diagnosis of the inflammatory reaction The changes can be shown by direct or in direct quantification methods of different fractions. The indirect methods measure phenomena which at least partly follow the increase of the acute phase protein con centration The most important of these methods is the erythrocyte sedimentation rate. The determination of C-reactive protein concentration is frequently used in clinical diagnosis because this protein is not present in the healthy body (47 140) The plasma concentration of haptoglobin can be deter mined by relatively simple chemical methods, and therefore it has been used to reveal the inflammatory process (1)

b. Newborn Infants and Infections

Infections of the newborns form their own group because the means of transmission, clinical picture and prognosis are different from those of adult infections (147) Rubella virus was the first infective agent noted to be able to invade the fetus through the placenta and cause fetal infection (61) In addition, several other viruses and some bacteria, protozoa and spirochetae can be transmitted from the maternal blood cir culation through the placenta to the fetus and infect the fetus during intrauterine life (intrauterine or prenatal infection) An in dividual who has had an intrauterine in fection may be a microbe carrier for a long time (158)

Transmission is also possible during deliv ery when the neonate receives the micro-organism from the maternal pelvic canal (intranatal infection) The neonate can also be infected after delivery with transmission via the surroundings (postnatal infection) (147)

There are several weak points in the resistance and immunological reaction to infections of newborn infants The infant receives the maternal immunoglobulins only of IgG type through the placenta. Thus the child is susceptible to several gram-negative bacilli whose antibodies are mostly of the IgM type It is natural that a newborn child is incapable of producing a secondary response in antibody formation, because all in fections in this age group are primary in fections There are also defects in the unspecific components of infection resistance in the neonate The clinical picture of infections in neonates is varied and, correspondingly problems in diagnosis are great compared with adults

Phagocytosis The leucocyte and especially neutrophilic granulocyte count in the periph eral blood of neonates is higher than that of adults Unlike that of adults the granulocyte count in neonates may often decrease in infections. The granulocytes of neonates have a phagocytic property (1)

Fever The significance of fever in diag nosis of infections is not as great in neonates as in adults and older children because the temperature regulation of neonates is not fully developed. A neonate with an infection can be febrile or have a normal temperature or even be hypothermic (147)

Immunological Reaction The fetus and the neonates can produce immunoglobulins after antigenic stimulation mainly of IgA and IgM type. Cell mediated immunity also develops during the intrauterine life against antigens which have invaded the body The synthesis of immunoglobulins has been observed as early as in the 10th week of fetal life (35 57) In principle the immunological reaction due to an intrauterine, intranatal or postnatal infection is identical with the primary reaction in later infections.

Acute Phase Reaction The synthesis of acute phase proteins starts very early during fetal life at least from the 8th to 9th week onwards (57) There are however fairly few

does not depend on e.g changes in environmental pH Haptoglobin itself does not have peroxidase activity but haptoglobin hemoglobin complex has been suggested to have a true peroxidase activity (110)

d. Methods of Determining Concentration and Type of Haptoglobin

A Qualitative Determination of Haptoglobin

1 The most important methods of determining haptoglobin type are based on the different molecular sizes of haptoglobins The types can be distinguished by electrophoresis in a media which has sieving effect (152) In gel electrophoresis (starch, polyacrylamide polymerized cellulose acetate agarose etc.) the haptoglobin molecules of different sizes have different mobility The quantitative ratios and the numbers of fractions with different mobilities vary according to the genetic type Staining of the haptoglobin fractions after the electrophoretic run can be carried out by several techniques the most frequently used stains being o-dianisidine and benzidine (e g 136)

2 The genetic haptoglobin types can also be detected by immunochemical methods. The most useful method is crossed antigen-antibody electrophoresis (98) which is based on the difference in electrophoretic mobility of the different types

3 The haptoglobin subtypes can be determined by electrophoresis after breaking down to polypeptide chains. Usually this is done by urea formate starch gel electrophoresis (3° 1 3)

4 The detection of subtypes has also succeeded immunochemically by subgroup-specific antisera (45 46)

B Quantitative Determination of Haptoglobin

The quantitative estimation methods can be divided into groups according to the properties of haptoglobin on which they are based.

1. Methods based on the properties of haptoglobin-hemoglobin complex:
   a. ability to enhance the peroxidase activity of hemoglobin
   b changes of electrophoretic mobility
   c changes in precipitation by ethacridin (Rivanol®)
   d gel filtration
   e protection of spectral properties against acid denaturation
2. Immunochemical methods

1 All methods in this group are based on adding free hemoglobin to the specimen. Therefore it is important to see if an incorrect amount or type of hemoglobin causes changes in results (122) Free hemoglobin in the specimen (hemolysis) has an effect on all methods in this group If very exact results are required, normal hemolytic process in sampling which can give a hemoglobin concentration of about ~ mg/l must be taken into account (41)

a Methods for Measuring Peroxidase Activity

Hemoglobin has weak peroxidase activity When haptoglobin hemoglobin complex is formed the activity increases remarkably (110) Hemoglobin loses its own activity in acidic surroundings whereas the complex maintains it even in low pH values. Methods to determine haptoglobin based on this property are many They are divided into two groups The saturation method measures the amount of specimen which can bind a known quantity of hemoglobin. The parameter to be evaluated is the ability to increase peroxidase activity of the specimen. Thus the greatest amount of specimen which is still able to increase activity is estimated With this estimation and the concentration of the hemoglobin reagent used the hemo-

globin binding capacity of the specimen can be calculated (136)

In the activation method, peroxidase activity of the specimen is measured by adding a known amount of hemoglobin reagent to the specimen. The quantity of hemoglobin must exceed hemoglobin binding capacity of the specimen. Since hemoglobin has weak peroxidase activity the milieu must be acidic in order to prevent the activity of hemoglobin (157)

In both estimation techniques a method for measuring the peroxidase activity is needed. Therefore there are several modifications of this method to measure haptoglobin concentration. The source of oxygen is usually either hydrogen peroxide or ethylen hydroperoxide and the electron donor iodine o-dianisidine guaiacol, o-toluidine or p-phenylendiamine (78 105 106 114 157)

b Methods Based on Changes in Electrophoretic Mobility

The method is based on difference in electrophoretic *mobilities between haptoglobin* hemoglobin complex and its free components. Modifications vary most often with respect to the electrophoresis media and quantitation methods. All regular electrophoretic media can be used in which the haptoglobin-hemoglobin complex differs from hemoglobin. paper (74, 100) cellulose acetate (31 129) starch gel (0) agar and agarose (17) polyacrylamide (48) and plaster of Paris ( )

For estimation the saturation method can be used in which increasing amounts of hemoglobin are added to a series of the same sample Finally the hemoglobin binding capacity is exceeded, and the band of free hemoglobin is noted (17) This method is rather inconvenient because several parallel runs must be performed. Thus the method is not appropriate for numerous samples.

In staining methods free hemoglobin, haptoglobin hemoglobin complex and met-albumin separated by the electrophoretic run are stained and the colour intensities of the fractions are measured by densitometry or elution. Hemoglobin binding capacity of the specimen is calculated with these data The staining is usually done with benzidine o-dianisidine o-toluidine and p-phenylendiamine (130) The estimation of the fractions can also be carried out by turbidimetry (43) or radioactive markers (143) A quick and relatively accurate method is to scan the unstained fractions at 410 nm (1 9) or at 470 nm (108)

Disc electrophoresis has been employed as a semiquantitative method. The estimation is performed by scanning the gel after staining, and simultaneously it is possible to estimate the haptoglobin type (4)

c Changes in Precipitation by Rivanol®

Rivanol® (ethacridin) precipitates haptoglobin-hemoglobin complex, but free hemoglobin stays in the supernatant Other proteins do precipitate with this chemical. *The estimation is carried out by adding* hemoglobin until binding capacity is exceeded. The hemoglobin in the supernatant after precipitation with Rivanol® is measured. The method is not accurate, but it is convenient for serial determinations (93).

d. Gel Filtration

The haptoglobin hemoglobin complex is separated from free hemoglobin by gel filtration with *Sephadex G 100 Estimation* is made by measuring the bound hemoglobin or the ratio of free and bound hemoglobin to the total hemoglobin amount. The first-mentioned method is more accurate with a hemolyzed sample (70) On the other hand increased bilirubin concentration and lipemia are sources of error in this case (62) The method is accurate but is not suitable for serial determinations or for neonates because of the physiological icterus.

c Methods Based on Protection of Spectral Properties

The absorbency of hemoglobin solutions at 407 nm falls rapidly to approximately half of the initial value at pH 3 7 (141) The absorbency of hemoglobin in the complex is the same as that of free hemoglobin and the changes of pH have no influence on it The greater the amount of haptoglobin in the sample added to hemoglobin reagent, the less the absorbency decreases with decreased pH The method is accurate also in low con centration (141)

2 All haptoglobin types have sufficiently common antigenic determinants in order to be able to use all haptoglobin antisera for immunochemical estimation methods. The haptoglobin types have, however certain antigenic differences (94) among other things various epitopes (75 76) These differences cause inaccuracies in immunochemical deter mination but it is not significant in clinical work (149)

All regular immunochemical protein esti mation methods can be used with hapto-globin (3 13 93 99 109) The different molecular sizes of haptoglobins affect the results given by the methods which are based on diffusion in gels Thus diffusion rates in gel vary from one type to another The results can be directly used only when the antiserum used, the standard solution of haptoglobin and the specimen are of the same type. In other cases mixed standards and mixed antiserum must be employed and the specimen has to be classified and the result calculated depending on the hapto-globin type used (23)

C. REFERENCE VALUES OF PLASMA HAPTOGLOBIN CONCENTRATION

a. Reference Values for Adults

The variation of reference values for adults is great (80) On the other hand, the con centration does not change in the plasma of the individual unless there are other factors involved. Healthy persons have often small infections which are not diagnosed. This may be the cause of variation in one individual (80) This may also explain the wide range of reference values.

The various methods also give rise to different reference values in the literature. The immunochemical methods based on gel diffusion require determination of hapto-globin types. Since this is not always done inaccurate results due to different molecular sizes based on the genetic type may occur (13 156) Despite this, the chemical methods yield correct results. However there is con fusion whether the result should be given as haptoglobin or hemoglobin binding capacity (80 122) A summary of reference values for adults is in Table 1

b Physiological Factors Influencing Haptoglobin Concentration

1 Genetic factors. The concentration of Hp 1—1 is usually higher than that of Hp 2—2 (121) It has been shown with twin studies that haptoglobin concentration is also under other genetic control (150) This is confirmed by the familial occurrence of hypohaptoglobinemia (117)

2. Sex differences and hormonal influence. There are distinct sex differences in the plasma haptoglobin concentration (1**) The reference values for women are lower than for men. The estrogens decrease haptoglobin concentration which is clearly seen during the menstruation cycle (122) and in women who use oral contraceptive steroids (154) In puberty certain differences have been noted but these have not been confirmed (107)

3 Age variation. After childhood there is no greater variation in haptoglobin con centration. It has been stated that the con centration increases with age decreasing however again after 70 (107)

Table 1 *Haptoglobin concentration in the plasma of normal adults*

Author	Method	Hp-type	Hp concentration g/l mean	SD	range
Nyman (122)	Peroxidatic (HbBC)	All	1.43	0.53	0.36–[illegible]60
		1–1	1.77	0.59	1.00–[illegible]
		–1	1.40	0.45	0.41–[illegible]30
		–2	1.07	0.44	0.19–1.94
Allison (6)	Starch-gel electrophoresis (HbBC)	1–1	1.58	0.34	
		–1	1.56	0.34	
		2–2	1.30	0.36	
Korinek (93)	Rivanol[R] precipitation (HbBC)	All	1.46	0.47	0.39–[illegible]40
		1–1	1.71		0.91–[illegible]40
		2–1	1.61		0.45–[illegible]40
		2–2	1.30		0.39–[illegible]40
Störiko (156)	Radial immuno-diffusion (Hp)	2–1	1.80		0.10–2.20
Becker & al (13)	Radial immuno-diffusion (Hp)	All	type dependent		0.25–[illegible]20
Reference values for adults in our laboratory	Peroxidatic (HbBC)	not determined	1.33	0.56	0.50–2.20

Results given in hemoglobin-binding capacity (HbBC) are converted to g Hp/l by equation Hp = HbBC × 1.3.

c. Reference Values for Infants

By using gel electrophoresis for identification and estimation of haptoglobin type in cord blood of the neonates, haptoglobin has been found only in 20 per cent of cases (14, 16 20 26 51 52 55) When more sensitive methods have been used (e.g gel filtration or peroxidase activation methods) haptoglobin has been found in 60–70 per cent of cases (1 65 69 132 133 151 159 169 175) In addition to insensitivity of the methods, there is another reason for the missing haptoglobin of newborn infants. According to this theory haptoglobin in neonates differs from that of adults It does not bind to hemoglobin in the normal way but it still reacts with the antisera for adult haptoglobin (49) This might explain the exceptionally low concentrations found by chemical methods.

According to some investigations the synthesis of haptoglobin begins in early intrauterine life (35, 57 69 159) but there are also contradictory observations (16) It has been shown by isotope technique that a human fetus synthesizes haptoglobin in the liver as early as at the age of nine weeks (57) The gestation age has no influence either on the haptoglobin concentration of neonates, or on the level variations after delivery (132 133) On the other hand, there is one study which has found a difference between premature and full term infants (10) There are hardly any reports on haptoglobin in pathological deliveries The haptoglobin concentration of neonates of pre-eclamptic mothers is the same as that of normal neonates. Differences in some other plasma proteins have been observed (155) It is obvious that strong haptoglobin synthesis

begins in the neonatal period. The plasma haptoglobin concentration rapidly increases during the first days (e.g. 52, 132, 137). The rate of the increase varies from day to day. At the age of 3—5 days the increase is very high (169). At the end of the first week (159) and at the age of 10—15 days (44) the concentration temporarily decreases.

The lower limits of adult reference values are usually reached during the first weeks, though the mean reference values are reached only at the age of some years (44, 109). It is interesting that plasma haptoglobin concentration decreases somewhat at the age of 4—5 years and stays there for rather a long time (44). A summary of reference values for infants and children is seen in Table 2.

Table 2. *Haptoglobin concentration in the plasma of normal infants and children*

Author	Method	Age	Hp-concentration g/l (Hp or HbBC) mean	SD	range
Weippl (168)	Electrophoretic (HbBC)	3— 6 m	0.85		0.55—1.20
		6—12 m	1.03		0.60—1.25
		1— 3 y	0.95		0.55—1.40
		3— 6 y	1.10		0.70—1.50
		6— 9 y	1.05		0.70—1.40
		9—1 y	1.00		0.75—1.35
Sklavunu Zurukzoglu & Malaka (151)	Peroxidatic (HbBC)	1—12 m	0.97		
		2 y	1.00		
		3 y	1.09		
		4 y	0.91		
		5 y	0.89		
		6 y	0.96		
		7 y	0.92		
		8 y	1.04		
		9 y	0.92		
		10 y	1.10		
		11 y	1.01		
		12 y	0.81		
		13 y	1.10		
		14 y	0.[illegible]		
Abrams & Freeman (1)	Immunochemical (values expressed as percentage of reference serum)	cord	4.2	0	
		1 d	8.1	21	
		2 d	48	45	
		4 d	85	67	
		1 m	66	48	
		1 m	82	67	
		2 m	123	87	
		3 m	207	78	
		6 m	235	125	
Trowitzsch & al. (159)	Immunochemical (values expressed as percentage of reference serum)	cord	18.3		0.25—120.0
		1— 2 d	7.6		0.25— 27.5
		4— 5 d	18.8		0.25— 65.6
		7— 8 d	20.8		0.25—114.5
		2 w	16.5		0.25— 85.0
		3 w	10.8		0.25— 60.6
		4 w	—		0.25— 9.4

Table 2 (continued)

Author	Method	Age	Hp-concentration g/l (Hp or HbBC) mean	SD	range
Philip (133)	Peroxidatic (HbBC)	cord	0.21		0.11–0.50
		5 d	0.52		0.15–1.00
Philip (133)	Peroxidatic (HbBC)	cord	0.11		
		5 d	0.30		
		10 d	0.20		
		15 d	0.16		
		21 d	0.05		
		28 d	0.12		
Bergstrand & al. (16)	Peroxidatic (HbBC)	1½– 2 m	0.20		0.00–0.78
		3– 4 m	0.45		0.00–0.80
		5– 6 m	0.44		0.00–1.45
		7– 8 m	0.66		0.18–1.83
		9–12 m	0.92		0.22–1.99

D HAPTOGLOBIN IN PATHOLOGICAL CONDITIONS

Reviews of haptoglobin concentrations in pathological conditions are many (22 122 128, 136) Therefore only problems of special interest to the present study are discussed.

a. Plasma Haptoglobin Concentration in Liver Diseases

Since *haptoglobin synthesis mostly takes* place in the liver (16) plasma haptoglobin concentration in hepatocellular lesion decreases, as do the concentration of other proteins synthesized by the liver In all hepatocellular lesions like hepatitis cirrhosis and toxication of the liver plasma haptoglobin concentration is low (68 122 128) This depends both on the decreased synthesis of haptoglobin and on changed circumstances in the circulation of the liver which allow *mechanical hemolysis in the vessels of the* organ (122) In obstructive jaundice haptoglobin concentration increases. The reason for this is apparently the destruction of biliary ducts with an acute phase reaction (1 7 134)

b. Plasma Haptoglobin Concentration in Hemolytic Disorders

The haptoglobin concentration always decreases when there is free hemoglobin in the intravasal space irrespective of the cause of hemolysis (1* 25 67 104) The decrease is similar if hemolysis has been produced mechanically or by disease (71 125)

Haptoglobin completely *disappears* from plasma if the amount of free hemoglobin is twice that *of normal conditions* (25 123) Hemoglobin injections also cause haptoglobin concentration to decrease Also in connection with extravascular hemolysis the decrease of plasma haptoglobin is seen (26)

Investigations of plasma haptoglobin concentrations in neonates in many cases deal with hemolytic conditions. Special attention must be paid to studies on haptoglobin concentration in connection with exchange transfusions. After exchange transfusion the concentration *is almost as high as* in adults but it quickly decreases to the initial level before starting to increase again (104 169). These investigations were performed on neonates with Rh immunisation The correlation between the decreasing rate and

IV MATERIAL AND METHODS

A PATIENTS

Most of the patients were neonates treated in the Children s Hospital University of Turku Turku Finland in the ward for new born infants The material was collected from June 1969 to January 1973 Approximately 20 per cent of the children were excluded for technical reasons mostly because it was not possible to obtain sufficient blood.

The second group consisted of healthy neonates from whom samples were obtained from the umbilical cord and at the age of 1—2 days The samples were taken from children of healthy mothers after a normal delivery The group includes only infants who were born in the morning because the samples were taken along with routine samples.

The third group consists of neonates who were treated in the years 1967—1969 in the Children s Hospital University of Helsinki Helsinki, Finland, for intrauterine infection.

In all 1220 samples from 600 neonates were investigated. Table 3 shows the patients and the control group divided into different subgroups according to criteria presented in the following

1 In addition to cord blood samples the control group results of two subgroups. The smaller of these subgroups included healthy neonates after normal deliveries.

Haptoglobin concentration was determined from a serum sample taken at the same time as normal bilirubin determination. No other laboratory parameters were estimated at this time because the children were healthy and an attempt was made to avoid taking unnecessary samples.

The other subgroup consists of hospitalized infants who showed no clinical or labora tory signs or symptoms of infections, nor had they had an exchange transfusion The indications for hospitalization are seen in Table 4

2. Neonates with intrauterine infection.

Table 3 *The material of this study*

1. Comparison group		293
) healthy newborns	1	
b) hospital patients	24	
) cord blood	90	
2. Newborns with intrauterine infection		29
3. Newborns with postnatal infection		79
4 Newborns with septicaemia		73
5. Newborns with exchange transfusion due to ABO immunization		23
6 Newborns with exchange transfusion due to Rh immunization		27
7 Newborns with exchange transfusion due to hyperbilirubinaemia without isoimmunization		134
8. Newborns with suspected infection		32
Total		690

Table 4 *Cause of hospitalization of the comparison group*

1 Neonatal asphyxia	40
2. Prematurity	56
3. Suspected congenital heart disease	27
4. Prolonged jaundice	13
5. Maternal diabetes or hypoglycemia of the newborn	18
6. Mongolism	6
Maternal toxemia	
8. Other causes	18
Total	[illegible]

In order to be included in this group an infection was diagnosed by antibody determination and/or virus isolation. All children had to show clinical symptoms of infection. tiredness, inactiveness cyanosis or greyness, fever or hypothermia, thrombocytopenia IgM concentration over 0 30 g/l, specific rash in some cases malformations The etiology of the infections is seen in Table 5 Neonates with unknown etiology of infection are included in this group because the clinical picture and history confirm the diagnosis.

Table 5 *Etiology of intrauterine infection*

1 Coxsackie B 4 virus	6
2. Cytomegalo virus	6
3. Rubella virus	5
4. Herpes simplex virus	5
5. Adenovirus 7	1
6. Treponema pallidum	1
7 Toxoplasma gondii	1
8. Etiology unknown	4
Total	29

3 Neonates with postnatal infection. This group consists of infants with clinical signs of infection and repeatedly isolated infective agent. Neonates without clinical signs but from whom infective agents were repeatedly isolated are also included here Clinical diagnoses of these infants are presented in Table 6

Table 6 *Diagnosis of neonates with postnatal infection*

1. Respiratory infection (incl. clinically healthy)	29
2. Neonatal impetigo	16
3. Urinary tract infection (incl. clinically healthy)	14
4. Infection of the umbilicus	8
5. Generalized viral infection	6
6. Meningitis	5
7 Oral candidiasis	2
8. Carditis	1
Total	79

4. Neonates with septicaemia. Infants with clinical signs of septicaemia and positive blood culture are included in this group Seven neonates, however with negative blood culture are also included. In four of these cases blood culture was not successful because of technical error A repeated culture was always negative due to the commencement of antibiotic therapy Septicemia was positively diagnosed on the basis of the clinical picture and other laboratory data. the platelet count was under 100000×10^6/l and IgM concentration above 0 30 g/l. In addition, antibiotics had a favorable effect on all of these patients. Twelve children in this group were victims of a septicaemia epidemic due to streptococcus beta-hemolyticus. Table 7 shows the etiology of septicaemia.

Table 7 *Etiology of septicaemia*

1. Streptococcus beta-hemolyticus	14
2. Staphylococcus aureus	1
3. Escherichia coli	1
4. Etiology unknown	7
Total	23

5 Neonates on whom exchange transfusion was performed due to ABO immunization. The criteria were high bilirubin concentration with respect to age and birth weight, blood groups suitable for immunization, reticulocyte count over 10 per cent, and hemoglobin concentration below 150 g/l in some cases.

6 Neonates on whom exchange transfusion was performed due to Rh immunization. The criteria were positive Coomb s test, anti Rh antibodies in the mother blood groups suitable for immunization, reticulocyte count over 10 per cent, hemoglobin concentration below 150 g/l and high bilirubin concentration with respect to age and birth weight.

7 Neonates on whom exchange transfusion was performed without isoimmunization. All infants on whom exchange transfusion had been performed due to high bilirubin concentration with respect to age

and birth weight and in whom there was no isoimmunization belong to this group

8. Neonates with suspected infection. The children in this group had some signs or symptoms of infection but the diagnosis was *not confirmed. The symptoms of infection* are presented in Table 8

Table 8 *Criteria for grouping patients with suspected infections*

1. IgM concentration above 0.20 g/l, but no other symptoms or signs of infection	11
2. Only one positive culture from respiratory tract	7
3. Strong suspicion for infection, without laboratory confirmation	6
4. Only one positive culture from urinary tract	4
5. Only one positive culture from skin	3
6. Maternal rubella	1
Total	32

B BLOOD SAMPLES

The cord blood was taken immediately after cutting the umbilical cord. Mechanical pressure of the cord was avoided during sampling Blood samples in connection with exchange transfusion were taken from an umbilical catheter and thus the blood came from the umbilical vein or vena cava depending on the location of the catheter

The other samples were capillary samples by heel puncture without arteriolization. Even hemolytic samples were included.

Immediately after they were taken the samples were treated further for hematological investigations. For determination of bilirubin haptoglobin and IgM concentration the serum was separated immediately after clotting For hematological investigations of cord blood an EDTA sample was taken

All concentration estimations except haptoglobin and IgM were performed immediately Haptoglobin concentration was determined within a week after sampling The samples were stored at −20°C The IgM concentrations were determined within 1—3 days after sampling and the samples were stored at +4°C or −20°C

C LABORATORY METHODS

a. Estimation of Haptoglobin

The haptoglobin concentrations given in this work indicate hemoglobin binding capacity (HbBC) of the sample in g hemoglobin/l.

A method based on enhancing peroxidase activity was chosen for the estimation of haptoglobin concentration (157) Horse hemoglobin was used instead of human hemoglobin. The o-dianisidine reagent was prepared in acetate buffer pH 4 1

The estimation of haptoglobin concentration was made as follows 10 μl of serum or standard solution of haptoglobin was added to 50 μl of the hemoglobin reagent and mixed. After 10 minutes 20 μl of the solution was added to 5 ml of o-dianisidine reagent mixed and allowed to stand for 15 minutes. After this, 1 ml of ethylene hydroperoxide was added and the mixture was incubated for 60 minutes at room temperature Then three drops of concentrated o-phosphoric acid were added and after thoroughly mixing the absorbency at 395 nm was immediately measured with the Beckman B photometer

The blank was prepared as described above but physiological saline was added instead of serum or standard solution.

The concentration of haptoglobin in the sample was calculated according to the following equation.

concentration (HbBC) =

$$\frac{\text{absorbency of sample}}{\text{absorbency of standard}} \times \text{concentration of the standard.}$$

The reagents were as follows:

1 Horse hemoglobin solution. The stock solution was made by hemolyzing washed horse erythrocytes with saponin and distilled water and freezing The hemoglobin concentration of the solution was 85 g/l Before use the stock solution was diluted to a concentration of 0 6 g/l with physiological saline

2 The o-dianisidine reagent The acetate buffer was made by adding 0 5 g of sodium EDTA (Titriplex) 2.0 g of anhydrous sodium acetate and 2.2 ml glacial acetic acid to 1000 ml of distilled water The pH value was adjusted to 4.1 ± 0.05 with glacial acetic acid or sodium hydroxide To 1000 ml of the buffer 1 0 g of o-dianisidine (Eastman Kodak, USA) was added. The reagent was left standing at room temperature After 24 hours it was filtered and then again always before use

3 Ethylene hydroperoxide 10 solution of ethylene hydroperoxide (Ferrosan Sweden) was diluted in proportions of 1 100 with distilled water

4 Haptoglobin standard. Lyophilized haptoglobin (Kabi Sweden) was dissolved in physiological saline to a concentration of 1 00 g/l (hemoglobin binding capacity) The hemoglobin binding capacity was measured by gel filtration using a Sephadex G-100 column for the separation of haptoglobin hemoglobin complex and free hemoglobin

The method was compared with a single radial immunodiffusion method (109) The plates were made of 1.5 % agarose A mixed rabbit antihuman haptoglobin serum was used (Behringwerke Ag, West Germany) The presence of haptoglobin in cord blood was investigated by double immunodiffusion method.

Plasma haptoglobin concentration was measured in some of the samples also with the Rivanol® precipitation method (93)

b. Other Laboratory Methods

Hemoglobin concentration was measured by the cyanmethemoglobin method (38) The platelets and leucocytes were counted in a chamber or by an electronic counter (Coulter-Counter) (39 40) An optic counter (SMA 7) was also used for counting leucocytes (39) The reticulocytes were counted by using vital staining with brilliant cresyl green (37) Concentration of bilirubin was measured by diazo reaction with a manual or automatized modification (82) The IgM concentration was determined by the single radial immunodiffusion method of Mancini (109) or by a modification of it (174) The plasma hemoglobin concentration was measured from the absorption spectrum

D STATISTICAL METHODS

The statistical calculations for comparison of the concentrations were performed by using Student s t test If the probability of error p was in the range $0.01 < p \leq 0.05$ the difference was regarded as nearly significant if $0.001 < p \leq 0.01$ the difference was significant if $p \leq 0.001$ the difference was highly significant

V RESULTS

A. ESTIMATION METHOD OF HAPTOGLOBIN

a. Precision of Method

The precision of the present method (157) was investigated by estimating the concentration of three standard samples along with routine samples ten times. The estimations were carried out at different times during the investigation thus giving day-to-day precision. The mean values, standard deviations and variation coefficients were as follows:

I mean ± SD = 1.46 ± 0.05 g/l VC 3.7%
II mean ± SD = 0.71 ± 0.02 g/l VC 2.5%
III mean ± SD = 0.09 ± 0.01 g/l VC 2.1%

In order to calculate the within-run precision the concentration of one standard serum was estimated seven times in the same series. The result was as follows:

mean ± SD = 1.72 ± 0.01 g/l VC 0.58%

b. Accuracy of Method

The accuracy of the present method was investigated by twice estimating the concentration of five samples, which were made of stock solution with a concentration of 1.00 g/l. Each time two parallel estimations were made. The stock solution was made in the same way as the standard used but the batch of haptoglobin was different. The recovery of these determinations was calculated. The results are seen in Table 9.

Table 9 *Recovery of haptoglobin by Tarukoski method (157)*

Calculated concentration g/l	Recovery % estimation I	II	mean
1.00	97	99	98.0
0.50	94	93	93.5
0.17	97	94	95.5
0.09	79	83	81.0
0.06	91	75	83.0

c. Effect of Hemolysis and Comparison with Other Methods

The haptoglobin concentration was estimated by the present and immunodiffusion methods in five pooled samples each of which was prepared from five random serum samples (Table 10). To investigate the effect of hemolysis in both methods increasing amounts of human hemoglobin were added to serum samples. In one sample where hemoglobin was added the determinations were made only by the present method. The results are given in Table 10.

Hemolysis disturbs both methods. In the case of immunodiffusion, increase in hemoglobin concentration gives excessively high results for haptoglobin. In the present method, the presence of hemoglobin causes decrease of haptoglobin concentration. At a hemoglobin concentration of 600 mg/l the result of haptoglobin determination is about five per cent too low. In addition, the effect increases slowly with the increasing concentration of hemoglobin.

A series of random samples, both new born and adult sera, were analyzed for

Table 10 *Comparison of immunodiffusion method (109) and peroxidatic method (157) and effect of hemoglobin on determination of haptoglobin*

% = Hp concentration in percentages obtained by peroxidatic method from plasma without hemoglobin.
a = peroxidatic method.
b = immunodiffusion method.
Details see text p. 4.

Sample number	Hb conc. in plasma mg/l	Hp conc. by a) g/l	Hp conc. by a) %	Hp con by b) g/l	Hp con by b) %
I	0	1.70	100	1.76	103
	220	1.63	96	1.76	103
	520	1.66	98	1.67	99
	1050	1.41	83	ca 2.5	ca 150
	1600	1.41	83	ca 2.5	ca 150
II	0	1.67	100	1.80	108
	290	1.71	102	1.77	106
	560	1.53	92	1.72	103
	1070	1.50	90	ca 2.5	ca 150
	1500	1.50	90	ca 2.5	ca 150
III	0	1.53	100	1.60	104
	290	1.48	97	1.62	106
	570	1.40	92	1.67	109
	1070	1.32	86	ca 2.1	ca 140
	1100	1.33	86	ca 2.1	ca 140
IV	0	0.99	100	1.00	101
	290	0.90	91	0.98	99
	590	0.90	91	1.08	109
	1110	0.84	85	1.16	117
	1630	0.91	92	1.26	127
V	0	1.50	100	1.48	99
	200	1.54	103	1.48	99
	600	1.46	97	1.48	99
	1080	1.36	91	ca 2.1	ca 140
	1620	1.38	92	ca 2.1	ca 140
VI	0	1.18	100		
	50	1.20	102		
	80	1.18	100		
	160	1.18	100		
	400	1.10	93		
	830	1.06	90		
	1250	1.03	87		
	1800	1.09	92		

haptoglobin by the Rivanol[R] and the present method. Table 11 shows the results from adult samples compared with the results by the Tarukoski method. The plasma haptoglobin concentration of neonates could not be measured with the Rivanol[R] method because the absorbencies were *lower* than those of blanks. Concentrations of hemolytic samples were immeasurable for the same reason.

Table 11 *Comparison of a) peroxidatic method (157) and b) Rivanol[R] method (93)*

Haptoglobin concentration in g/l (HbBC) by	by b
1.18	1.70
2.25	3.12
0.58	1.04
0.12	measurement was not possible
0.06	—»—

d. Effect of Storage

The stability of haptoglobin during storage was investigated only at the temperature of +4°C. Six random serum samples were stored for 40 days in a refrigerator and haptoglobin concentration was determined at intervals. The results are seen in Table 12, which shows that small variations in haptoglobin concentration occur during the storage.

Table 12 *Effect of storage on haptoglobin concentration, temperature +4 C*

% = Hp concentration in percentages of the value obtained at time 0.

Time days	Concentration of sample I g/l	I %	II g/l	II %	III g/l	III %
0	1.1	100	0.43	100	1.1	100
3	1.2	109	0.42	98	1.2	109
30	1.2	109	0.48	112	1.3	118
40	1.3	118	0.60	140	1.4	127

e. Usefulness of Different Methods

The total time and the time for active work in determination of haptoglobin concen

V RESULTS

A. ESTIMATION METHOD OF HAPTOGLOBIN

a. Precision of Method

The precision of the present method (157) was investigated by estimating the concentration of three standard samples along with routine samples ten times. The estimations were carried out at different times during the investigation thus giving day to-day precision. The mean values, standard deviations and variation coefficients were as follows:

I mean $\pm$ SD = 1 46 $\pm$ 0 05 g/l VC 3 7%
II mean $\pm$ SD = 0 71 $\pm$ 0 02 g/l VC 2.5%
III mean $\pm$ SD = 0 69 $\pm$ 0 01 g/l VC 2.1%

In order to calculate the within-run precision the concentration of one standard serum was estimated seven times in the same series. The result was as follows:
mean $\pm$ SD = 1 72 $\pm$ 0 01 g/l VC 0 58%

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The accuracy of the present method was investigated by twice estimating the concentration of five samples which were made of stock solution with a concentration of 1 00 g/l. Each time two parallel estimations were made The stock solution was made in the same way as the standard used but the batch of haptoglobin was different. The recovery of these determinations was calculated. The results are seen in Table 9

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The haptoglobin concentration was estimated by the present and immunodiffusion methods in five pooled samples each of which was prepared from five random serum samples (Table 10) To investigate the effect of hemolysis in both methods increasing amounts of human hemoglobin were added to serum samples. In one sample where hemoglobin was added, the determinations were made only by the present method. The results are given in Table 10

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A series of random samples, both new born and adult sera, were analyzed for

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% – Hp concentration in percentages btained by peroxidatic method from plasma without hemoglobin.
 – peroxidatic method.
b – immunodiffusion method.
Details see text p. 24.

Sample number	Hb conc. in plasma mg/l	Hp conc. by a) g/l	Hp conc. by a) %	Hp conc. by b) g/l	Hp conc. by b) %
I	0	1.70	*100*	1 8	103
	220	1.63	96	1 76	103
	520	1.56	92	1.67	99
	1080	1 41	83	ca –.5	ca 150
	1600	1.41	83	ca 2.5	ca 150
II	0	1.67	100	1.80	105
	230	1 71	102	1.77	106
	560	1.63	93	1 72	103
	1070	1.50	90	ca 2.5	ca 150
	1600	1.50	90	ca 2.5	ca 150
III	0	1.53	100	1.60	104
	230	1 48	97	1.62	106
	570	1 40	93	1 67	109
	1070	1.32	86	ca 2.1	ca 140
	1100	1.33	86	ca 2.1	ca 140
IV	0	0.99	100	1.00	101
	290	0.90	91	0.98	99
	590	0.80	81	1.06	106
	1110	0.84	85	1.16	117
	1630	0.91	92	1.26	127
V	0	1.50	100	1 48	99
	200	1.54	103	1 48	99
	600	1.46	97	1 48	99
	1080	1.36	91	ca 2.1	ca 140
	1620	1.38	92	ca 2.1	ca 140
VI	0	1.18	100		
	50	1.20	102		
	80	*1 18*	*100*		
	160	1.18	100		
	400	1 10	93		
	630	1 06	90		
	1290	1 03	87		
	1800	1.08	92		

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Table 11 *Comparison of a) peroxidatic method (157) and b) Rivanol[R] method (93)*

Haptoglobin concentration in g/l (HbBC) by a	by b
1.18	1 70
2.26	2.12
0.53	*1.04*
0.12	measurement was not possible
0.06	– –

d. Effect of Storage

The stability of haptoglobin during storage was investigated only at the temperature of +4°C Six random serum samples were stored for 40 days in a refrigerator and haptoglobin concentration was determined at intervals. The results are seen in Table 12 which shows that small variations in haptoglobin con centration occur during the storage

Table 12. *Effect of storage on haptoglobin con centration temperature +4 C*

% – Hp concentration in percentages of the value obtained t time 0.

Time days	Concentration of sample I g/l	I %	II g/l	II %	III g/l	III %
0	1 1	100	0.43	100	1 1	100
3	1.2	109	0.43	98	1.2	109
30	1.2	109	0.48	112	1.3	118
40	1.3	118	0.60	140	1.4	127

e Usefulness of Different Methods

The total time and the time for active work in determination of haptoglobin concen

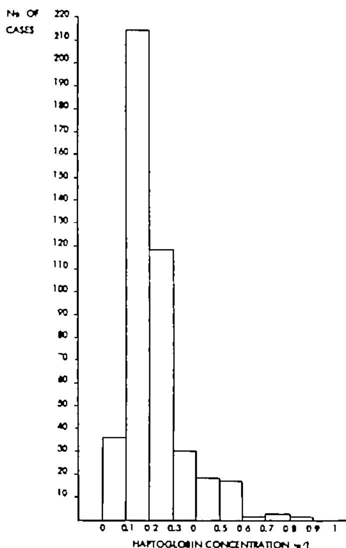


Fig 1 Distribution of haptoglobin concentrations in the comparison group.

tration by the different methods were investigated in order to reveal their suitability in circumstances in which speed is important. All results were achieved from one sample In the immunochemical method the time for classifying the haptoglobin samples is not included. The present peroxidatic method takes 90 minutes of which 30 minutes is active work. In the immunodiffusion method the result was available after 24 hours. The time for active work was as little as 10 minutes The time used in the Rivanol[R] method is the same as in the present method.

f Effect of Sample Volume on Reliability of Method

The present method has not before been adapted for capillary samples. Haptoglobin concentration was determined from a sample using sample volumes of 10 μl and 100 μl with 50 μl and 500 μl of hemoglobin reagent, respectively After this the determinations were performed in a similar fashion. The results of ten samples were identical by both methods within the limits of standard deviation

B. PLASMA HAPTOGLOBIN CONCENTRATION IN CONTROL GROUP

Haptoglobin concentration in the control group was determined in cord blood and in neonates of different ages. The results are presented in Table 13 Haptoglobin concentration of cord blood is significantly lower than in neonates aged 1—2 days. After the first week haptoglobin concentration seems to decrease but the difference is not significant In Figure 1 haptoglobin concentrations of the control group are presented in diagrammatic form. It is seen that the values do not follow the Gaussian distribution because there are too many high concentrations.

Table 13 *Haptoglobin concentration in neonates g/l (HbBC)*

Age in days	N of cases	Mean	SD	Range
cord	30	0.07	0.05	0.03—0.10
1— 2	185	0.20	0.08	0.07—0.66
3— 7	120	0.24	0.14	0.15—0.87
8—14	78	0.18	0.07	0.12—0.77
>14	8	0.18	0.07	0.12—0.52
Total	422	0.20	0.11	0.03—0.87

Hp concentration in cord blood is statistically highly significantly lower than in other age groups.

Since part of the control group had a catheter in the umbilical vein, the effect of catheterization and bacterial invasion connected with this procedure on haptoglobin concentration was investigated. In Table 14 the values obtained from newborn infants with and without catheterization are presented. Patients with the umbilical catheter have significantly higher haptoglobin concentrations. Despite this difference all patients in the control group are included in the present study

Maturity of the infant and intensity of intravascular hemolysis are factors with a potential influence on plasma haptoglobin concentration in neonates. In order to

Table 14 *The effect of the catheterization of the umbilical vein on haptoglobin concentration*

	Hp-concentration g/l (HbBC) No. of cases	Mean	SD	Range
with catheterization	90	0.24	0.14	0.10—0.87
without catheterization	24	0.19	0.09	0.07—0.77

The difference is statistically highly significant.

establish these correlations the comparison group was divided into six categories according to plasma haptoglobin concentration. 1 $\leq$ 0.09 g/l 2. 0.10—0.19 g/l 3 0.20—0.29 g/l, 4. 0.30—0.49 g/l, 5. 0.50—0.69 g/l 6. $\geq$ 0.70 g/l Table 15 presents the mean values and standard deviations in hemoglobin concentrations the amounts of reticulocytes bilirubin concentrations, gestation ages and birth weights. The results reveal that the present material does not yield statistically significant correlations between haptoglobin concentration and any parameter of maturity or hemolysis. Although statistical significances do not occur there is a trend that neonates with high haptoglobin concentrations have somewhat greater birth weights than the others. In addition, infants with the lowest haptoglobin concentrations also have the lowest bilirubin concentrations.

In the table the number of infants varies in different parameters because it was not possible to obtain a sample adequately large for examining all the parameters.

To find out whether having a control group of hospital patients has any significance for the reference values the plasma haptoglobin concentrations of healthy infants at the age of 1—2 days were examined. Table 16 shows that there are no statistically significant differences between the groups.

The cord blood was also examined by double immunodiffusion in order to see whether hemoglobin binding capacity of cord blood samples is due to haptoglobin.

Table 15. *The effect of degree of hemolysis and maturity of newborn on haptoglobin concentrations*

The infants are divided into groups according to the haptoglobin concentration: I ≤ 0.09 II 0.10–0.19, III 0.20–0.29 IV 0.30–0.49 V 0.50–0.69 VI ≥ 0.70. (g/l)

	I	II	III	IV	V	VI
Hb g/l	154.7	179.1	184.7	190.5	167.5	208.2
± SD	4.3	23.8	21.1	33.9	31.8	45.4
n	12	169	91	28	4	3
Bilirubin µmol/l	62.0	132.4	126.0	134.0	123.5	179.2
± SD	55.3	84.0	70.1	65.9	101.5	104.9
n	33	164	94	34	6	3
Reticulocytes %	4.8	3.9	3.3	4.4	3.4	6.6
± SD	2.6	3.3	2.9	2.7	–.6	7.8
n	31	177	86	4	4	2
Gestation age w	38.4	37.0	37.6	37.7	38.8	38.0
± SD	2.6	2.9	–.7	2.3	2.9	2.0
n	35	210	119	38	9	3
Weight kg	3.1.	2.78	2.73	3.02	3.48	3.93
± SD	0.85	0.75	0.73	0.70	0.77	1.0
n	34	224	122	38	9	3

Table 16. *Haptoglobin concentrations in healthy and hospitalized newborns g/l (HbBC)*

	No. of cases	Mean	SD	Range
hospitalized	482	0.20	0.11	0.07–0.87
healthy	21	0.22	0.15	0.07–0.73

Difference is not statistically significant.

Table 17 *The effect of sex on haptoglobin concentration*

	Hp conc g/l	SD	No. of cases
female	0.47	0.47	535
male	0.45	0.67	653

Difference is not statistically significant.

The sensitivity of the method is approximately 2 mg/l of haptoglobin. In 16 cases out of the 30 cord blood samples examined haptoglobin was detectable by the immunochemical method. In samples with immunochemically detectable haptoglobin hemoglobin binding capacity was not greater than in the other cord blood samples.

In order to reveal the potential sex differences plasma haptoglobin concentrations of different sexes in the total material were investigated. The results in Table 17 show that there are no significant differences

The role of delivery in induction of haptoglobin synthesis by tissue lesions in the newborn was examined The correlation between plasma haptoglobin concentration and the duration and method of delivery and loss of amniotic fluid was studied in a part of the control group On the basis of 100 infants it was concluded that delivery could not be said to have had an influence on the plasma haptoglobin level of neonates.

In the control group it was investigated whether healthy mothers had haptoglobin in the amniotic fluid. Five samples of amniotic fluid were obtained by amniocentesis and examined by the present method which gave

Table 18. *Plasma haptoglobin concentration of neonates with exchange transfusion before and after g/l (HbBO)*

		Comparison group	Newborns with ABO-imm.		Newborns with ABO-imm.		Newborns without isoimmunization	
			before	after	before	after	before	after
1– 2 d.	Hp-conc.	0.20	0.16	0.60	0.14	0.70	0.22	0.71
	SD	0.08	0.11	0.30	0.08	[illegible]	0.16	0.33
	n	188	16	17	20	33	58	60
3– 7 d.	Hp-conc.	0.24	0.17	0.67	0.23	0.93	0.22	0.71
	SD	0.14	0.12	0.29	0.23	0.67	0.19	0.29
	n	130	9	9	12	1	147	148
8–14 d.	Hp-conc.	0.18	–	–	–	–	0.11	0.65
	SD	0.07	–	–	–	–	0.01	0.01
	n	76					2	2
over 14 d	Hp-conc.	0.18	–	–	–	–	–	–
	SD	0.07	–	–	–	–	–	–
	n	8						
Whole material (incl. cord bloods)	Hp-conc.	0.20	0.16	0.63	0.18	0.79	0.22	0.71
	SD	0.11	0.11	0.25	0.14	0.40	0.18	0.31
	n	433	25	26	42	45	205	206

haptoglobin concentrations of 0.07±0.02 g/l. The double immunodiffusion method revealed haptoglobin in two samples.

C. PLASMA HAPTOGLOBIN CONCENTRATION IN NEWBORN INFANTS WITH EXCHANGE TRANSFUSION

Plasma haptoglobin concentration in newborn infants with exchange transfusion was investigated before and after the procedure and then daily for 2–7 days. Table 18 shows the results as a function of exchange transfusion and age of the infants. The results reveal that after exchange transfusion, haptoglobin concentration is *significantly higher* than before. The concentrations correspond to those of adults. There are no differences between the age groups.

The results show that in neonates who receive an exchange transfusion, haptoglobin concentrations are *lower before* the exchange transfusion because of ABO or Rh immunization than in those without isoimmunization. The differences are not, however, statistically significant. When the indication for exchange transfusion was hyperbilirubinemia without isoimmunization plasma haptoglobin concentration was higher than in the control group. In this case the difference was not statistically significant either. The concentration is, however, *significantly higher in newborn infants* with exchange transfusion due to hyperbilirubinemia without isoimmunization than in immunized newborns.

Figures 2, 3 and 4 show the changes in haptoglobin concentrations after exchange *transfusion in relation to the indication for* exchange transfusion. It is seen that haptoglobin concentration in neonates with exchange transfusion due to ABO immunization or hyperbilirubinemia without isoimmunization evenly decreases to the level *before the procedure*. The half-life of exogenous haptoglobin is 4.0 days in neonates

Table 15 *The effect of degree of hemolysis and maturity of newborn on haptoglobin concentrations*

The infants are divided int groups according to the haptoglobin concentration: I ≤ 0 09 II 0.10–0.19 III 0.20–0.29 IV 0.30–0.49 V 0.50–0 69 VI ≥ 0.70. (g/l)

	I	II	III	IV	V	VI
Hb g/l	164.7	179.1	184.7	190.8	167.5	208.3
± SD	4.3	23.8	21.1	33.9	31.8	45.4
n	32	169	91	28	4	3
Bilirubin µmol/l	62.0	132.4	126.0	134.0	123.5	179.3
± SD	55.3	94.0	70.1	65.9	101.5	104.9
n	33	164	94	34	6	3
Reticulocytes %	4.8	3.9	3.3	4 4	3.4	6.5
± SD	_6	3.3	2.9	2.7	_6	7.8
n	31	177	85	4	4	
Gestation age w	38.4	37 0	37 6	37 7	38.6	35 0
± SD	_6	2.9	2.7	2.3	2.9	2.0
n	35	216	119	35	9	3
W ight kg	3.12	2.78	2.73	3.03	3.48	3.93
± SD	0.85	0 5	0.73	0.70	0 77	1.0
n	34	224	122	38	9	3

Table 16 *Haptoglobin concentrations in healthy and hospitalized newborns g/l (HbBO)*

	No. of cases	Mean	SD	Range
ospitalized	432	0.20	0.11	0 07–0.87
ealthy	1	0.22	0.15	0.07–0 5

)ifference is not statistically significant.

Table 17 *The effect of sex on haptoglobin concentration*

	Hp conc g/l	SD	No. of cases
female	0.47	0.47	535
male	0.45	0.67	635

Difference is not statistically significant.

The sensitivity of the method is approximately 2 mg/l of haptoglobin. In 16 cases out of the 30 cord blood samples examined, haptoglobin was detectable by the immunochemical method. In samples with immunochemically detectable haptoglobin hemoglobin binding capacity was not greater than in the other cord blood samples.

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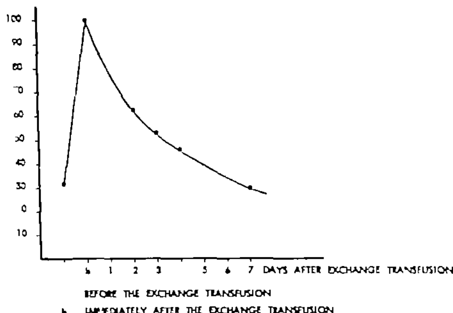


Fig 4 Changes in haptoglobin concentration in connection with exchange transfusion due t hyperbilirubinaemia without isoimmunization.

Table 19 *The correlation between haptoglobin and bilirubin concentrations in newborns with exchange transfusion*

The infants are divided into groups according t the haptoglobin concentration I ≤ 0.09 II 0.10–0.19, III 0.20–0.29 IV 0.30–0.49 V 0.50–0.69 VI ≥ 0.70. (g/l).

Cause of exchange transfusion	Bilirubin μmol/l					
	I	II	III	IV	V	VI
ABO-immunization	318.5	311.5	276.8	250.0	–	
SD	83.9	150 4	86.1	100.2	–	–
n	8	11	2	4	–	–
Rh immunization	98 9	230.0	207.5	127.0	367.0	–
SD	63.0	130.8	146.4	53.7	0.0	
n	10	21	2	2	1	
Hyperbilirubinemia without immunization	240.0	235 4	242.0	204.3	212.7	231 1
SD	47.3	56.8	71.9	101.7	52.9	49 7
n	36	99	23	19	14	8

Table 19 shows the correlation between bilirubin and haptoglobin concentrations. The infants are divided into groups according to haptoglobin concentration before exchange transfusion. 1 ≤ 0 09 g/l, 2 0 10–0 10 g/l 3 0.20–0 29 g/l, 4 0.30–0 49 g/l, 5 0.50–0 60 g/l, 6. ≥ 0 70 g/l. Tho results indicate that the bilirubin concentration is lowest in the group with the lowest haptoglobin concentrations. Except for this, there is no significant correlation between haptoglobin and bilirubin concentrations.

Table 20 *Haptoglobin concentration in neonates with infection g/l (HbBO,*

Type of infection		Age in days 1–2	3–7	8–14	14	Total
Intrauterine infection	Hp concentration	0.71	0.92	0.64	0.64	0.72
	SD	0.33	0.48	0.24	0.60	0.40
	range	0.23–1.60	0.30–1.65	0.36–1.35	0.22–0.70	0.22–1.6
	n	14	9	6	8	37
	significance t comparison group		**			**
Postnatal infection	Hp concentration	0.60	1.09	0.91	2.06	0.99
	SD	0.45	1.67	0.87	1.18	1.31
	range	0.14–2.28	0.14–3.06	0.21–3.05	0.40–3.1	0.14–3.12
	n	23	49	20	7	99
	significance to comparison group	***	**	**		*
Septicaemia	Hp concentration	0.77	1.40	1.53	1.77	1.45
	SD	0.58	0.86	0.66	2.09	1.14
	range	0.23–2.19	0.31–3.20	0.37–3.05	0.20–2.94	0.23–3.20
	n	6	14	12	8	40
	significance to comparison group	ns			ns	**
Suspected infection	Hp concentration	0.32	0.73	0.63	0.23	0.54
	SD	0.24	0.60	0.90	0.11	0.57
	range	0.09–0.70	0.12–0.93	0.10–1.60	0.15–1.48	0.09–1.60
	n	16	24	9	3	[illegible]
	significance to comparison group	ns		ns	ns	
Comparison group	Hp concentration	0.20	[illegible]	0.18	0.16	0.20
	SD	0.08	0.14	0.07	0.07	0.11
	range					
	n	188	130	76	6	433

– difference is statistically highly significant
– difference is statistically significant
– difference is statistically nearly significant
ns – difference is not statistically significant

D PLASMA HAPTOGLOBIN CONCENTRATION IN NEWBORN INFANTS WITH INTRAUTERINE INFECTION

Table -0 presents haptoglobin concentration in newborn infants with intrauterine infection The results are compared with haptoglobin concentrations of the control group in different age groups. Haptoglobin concentration in the youngest age group of infected neonates is statistically highly significantly higher than in the control group The difference is smaller in older age groups but it is significant in any case The range of haptoglobin concentration in sick infants is, however wide

To be able to compare other diagnostic parameters of infections and haptoglobin the material was divided into groups according to haptoglobin concentration. The results in Table 21 show that there is a correlation between IgM and haptoglobin con-

Table 21 *Correlation between haptoglobin concentration and Hb IgM and bilirubin concentrations and leucocyte and platelet counts in neonates with intrauterine infection*

The newborns are divided int groups, according to the haptoglobin concentration: I ≤ 0.09 II 0.10–1 19 III 0.20–0.29 IV 0.30–0.49, V 0.50–0.69, VI ≥ 0.70. (g/l).

	I	II	III	IV	V	VI
Hb g/l	–	–	122.0	164.6	199.5	123.4
SD	–	–	10.0	.5.0	23.3	5.0
n	–	–	2	10	6	14
IgM g/l	–	–	0.20	0.55	0.35	0.66
SD	–	–	0.14	0.32	0.35	0.61
n	–	–	2	11	6	13
Leucocytes × 10⁶/l	–	–	28700	14500	16900	13200
SD	–	–	23600	4500	8500	4000
n	–	–	2	8	7	12
Platelets × 10⁶/l	–	–	*231000*	*145000*	*216000*	*151000*
SD	–	–	231000	95000	167000	76000
n	–	–	2	8	6	13
Bilirubin μmol/l	–	–	–	234.8	206.7	161.3
SD	–	–	–	120.3	7 6	79.6
n	–	–	–	6	3	8

centrations. The higher the IgM level, the higher the haptoglobin level. The difference is not however statistically significant, but only a trend in that direction. As for the other parameters, no statistical correlations are observed.

Figure 5 shows haptoglobin and IgM con centrations and platelet and leucocyte counts in the control group and in infected neonates. It is apparent that although there is some overlap in haptoglobin concentrations in the various groups, the concentrations mostly give different values. In the other parameters, only IgM concentration shows a similar trend. The ranges of platelet and leucocyte counts are identical in all groups

E. PLASMA HAPTOGLOBIN CON CENTRATION IN NEWBORN INFANTS WITH POSTNATAL INFECTION

Table 20 presents haptoglobin concen tration in newborn infants with postnatal infection. The results are compared with those of the control group. The haptoglobin concentration of infected newborn infants is statistically significantly higher than that in all age groups of the control material. In this group as well, the difference is most obvious in the youngest age group.

The correlation between haptoglobin con centration and other parameters used in the diagnosis of postnatal infections is seen in Table 22. It reveals that the higher the haptoglobin concentration the higher also the IgM concentration In this case the dif ference is not statistically significant but only indicative There is no correlation between the other parameters.

Figure 5 reveals that newborn infants with postnatal infection show different haptoglobin concentrations from that of the control group A similar difference is seen in the IgM concentrations, too There are no differences in platelet and leucocyte counts between infected newborn infants and the control group

Table 20 *Haptoglobin concentration in neonates with infection g/l (HbBO)*

Type of infection		Age in days 1–	3–7	8–14	14	Total
Intrauterine infection	Hp concentration	0.71	0 92	0.54	0.64	0.
	SD	0.33	0.48	0.24	0.56	0.40
	range	0.23–1.00	0.30–1 65	0.36–1.35	0.23–0.70	0.22–1 65
	n	14	9	6	8	37
	significance to comparison group					**
Postnatal infection	Hp concentration	0 60	1.09	0.91	2.06	0.99
	SD	*0.45*	*1 67*	*0.87*	*1.18*	*1.31*
	range	0.14–2._8	0 14–3.06	0.21–3.06	0 40–3.1_	0 14–3.12
	n	23	49	20	7	99
	significance to comparison group			**		
Septicaemia	Hp concentration	0.77	1 40	1.53	1 77	1 43
	SD	0.66	0.86	0.66	2.09	1 14
	range	0.23–_.19	0.31–3.20	0.37–3.06	0.29–2.94	0.23–3.20
	n	6	14	12	8	40
	significance to comparison group	ns	**		ns	
Suspected infection	Hp concentration	0.32	0.73	0.53	0.23	0.54
	SD	0._4	0.38	0.90	0.11	0.57
	range	0 09–0.70	0 12–0.98	0.10–1.60	0.15–1 48	0.09–1 60
	n	16	24	9	3	52
	significance to comparison group	ns	***	ns	ns	
Comparison group	Hp concentration	0.20	0.24	0.18	0.16	0.20
	SD	0.06	0.14	0.07	0.07	0.11
	range					
	n	165	130	76	8	432

– difference is statistically highly significant
– difference is statistically significant
– difference is statistically nearly significant
ns – difference is not statistically significant

D PLASMA HAPTOGLOBIN CONCENTRATION IN NEWBORN INFANTS WITH INTRAUTERINE INFECTION

Table 20 presents haptoglobin concentration in newborn infants with intrauterine infection The results are compared with haptoglobin concentrations of the control group in different age groups. Haptoglobin concentration in the youngest age group of infected neonates is statistically highly *significantly higher than in the* control group The difference is smaller in older age groups but it is significant in any case. The range of haptoglobin concentration in sick infants is however wide

To be able to compare other diagnostic parameters of infections and haptoglobin the material was divided into groups according to haptoglobin concentration The results in Table 21 show that there is a correlation between IgM and haptoglobin con-

Table 22 *Correlation between haptoglobin concentration and Hb IgM and bilirubin concentrations and leucocyte and platelet counts in newborns with postnatal infection*

The newborns are divided into groups, according to the haptoglobin concentration: I ≤ 0.09 II 0.10–1.19, III 0.20–0.29, IV 0.30–0.49, V 0.50–0.69 VI ≥ 0.70. (g/l).

	I	II	III	IV	V	VI
Hb g/l	–	143.3	191.5	187.7	185.7	176.1
SD	–	37.5	12.8	22.4	27.5	23.8
n	–	4	6	24	16	34
IgM g/l	–	–	0.10	0.57	0.67	0.31
SD	–	–	0.00	0.65	0.70	0.25
n	–	–	1	7	6	13
Leucocytes × 10^6/l	–	14100	20500	13700	13000	13700
SD	–	4100	5300	6400	4700	7200
n	–	2	6	4	14	31
Platelets × 10^6/l	–	170000	204000	167000	167000	48000
SD	–	99000	57000	68000	80000	134000
n	–	2	6	23	13	23
Bilirubin µmol/l	–	257.0	161.9	149.6	158.2	144.0
SD	–	72.0	103.6	0.2	86.6	80.4
n	–	3	7	23	13	10

F PLASMA HAPTOGLOBIN CONCENTRATION IN NEWBORN INFANTS WITH NEONATAL SEPTICAEMIA

Table 20 shows haptoglobin concentration in newborn infants with neonatal septicaemia in different age groups contrasted with the control group According to the results haptoglobin concentration in age groups 3–7 days and 8–14 days is statistically highly significantly higher than in the control group In other age groups the difference is not statistically significant In the total septicaemia material the difference between sick and healthy infants is highly significant.

Table 23 presents the comparison between haptoglobin concentration and other diagnostic parameters of infections in infants with neonatal septicaemia. There are no statistically significant differences in any of the laboratory parameters A trend, however to higher IgM concentrations in neonates with high haptoglobin concentration is seen.

The changes in haptoglobin concentration in infants with neonatal septicaemia after beginning treatment is shown in Figure 6 Haptoglobin concentration decreases quickly immediately after commencement of treatment. The concentration decreases to 50 per cent of the initial value in approximately five days.

Haptoglobin and IgM concentrations before the treatment in neonates with septicaemia are given in Table 24. It is clear that haptoglobin concentration is elevated in all but one case and IgM concentration in two cases only

Figure 5 shows that in newborn infants with septicaemia, only haptoglobin and IgM concentrations differ from the values in the control group Leucocyte and platelet counts are identical in both groups.

Twelve of the neonates with septicaemia were infected in a ward epidemic of septi-

G PLASMA HAPTOGLOBIN CONCENTRATION IN NEWBORN INFANTS WITH SUSPECTED INFECTION

This group consists of patients who had some sign or symptom of infection, but diagnosis remained unclear due to lack of sufficient criteria The criteria for inclusion in this group are shown in Table 8 page 22.

Table 20 shows that haptoglobin concentration in neonates with suspected infection is higher than in the control group The difference is statistically significant in the age group of 3—7 days only In the total material the difference is highly significant

There were no significant differences in other laboratory parameters investigated in samples with different haptoglobin concentrations as Table 25 shows

Figure 5 shows haptoglobin and IgM concentrations and platelet and leucocyte counts in neonates with suspected infection compared with corresponding values of the control group As can be seen, the group is very heterogenous and all parametric values vary so much that no clear differences from the control group are noted, although haptoglobin concentration appears to be higher in infants with suspected infection.

VI DISCUSSION

A. ESTIMATION OF HAPTOGLOBIN

In the present study the indications for estimation of plasma haptoglobin concentrations were connected with hemolytic states and infections. Thus it could be expected that the concentrations to be measured were low However with infections the values may be rather high.

Certain basic requirements have been made for the method.

1 the method has to measure haptoglobin
2. the method has to be accurate enough in a wide concentration range mainly at low levels
3 the method has to be able to be used even with small amounts of sample
4 hemolysis in sampling must not effect the method essentially
5 the result has to be given quickly

The immunochemical methods measure only plasma haptoglobin concentration whereas the others, including the present peroxidatic method (157) give the hemoglobin binding capacity of plasma, which mainly is attributable to haptoglobin. In the present investigation the value 0 07 ± 0 05 g/l was achieved for haptoglobin concentration in cord blood. The present method revealed haptoglobin in all samples However the immunochemical methods show that as few as 16 out of 30 samples really contained haptoglobin. It is obvious that in cord blood, most of the hemoglobin binding capacity does not come from haptoglobin. It was observed that there was no correlation between haptoglobin concentrations achieved by immunochemical methods and the present method. It seems that hemoglobin binding capacity also varies with respect to components other than haptoglobin The results with these two methods are identical in high concentrations (Table 10) This has been confirmed by other investigations too (74) Obviously the present peroxidatic method measures all hemoglobin binding components but their part diminishes when the total binding capacity grows.

The difficulty in haptoglobin determination is that different laboratories have different standards for their methods. The result can be given as haptoglobin or hemoglobin binding capacity of plasma or serum, which adds to the confusion. The latter is more logical for methods based on peroxidase activity The values can, however be converted since 1 3 g of haptoglobin binds 1 0 g of hemoglobin (81) As a standard in the present study electrophoretically pure haptoglobin prepared by Kabi Ab Sweden was used. Its hemoglobin binding capacity had been estimated by a method based on gel filtration. A solution was prepared with hemoglobin binding capacity of 1 00 g/l Absorbency of the standard stayed practically unchanged during the present investigation. Commercial standard sera cannot be used because at least some of them contain preservatives that make it impossible to employ them in peroxidase activity methods (144). Unfortunately there is no international standard for haptoglobin as there is for immunoglobulins. For this reason

the reference values are individual for each laboratory

Because of accuracy requirements of the method and the low haptoglobin concentrations methods based on electrophoretic mobility (17 74) or Rivanol[R] precipitation could not be employed (Table 11) Gel filtration methods are difficult to use because they require a long time and special equipment

Immunochemical methods are appropriate (24) because they can be used with small amounts of sample they are haptoglobin specific and give results even in low concentrations However immunodiffusion methods are impractical here because the determination requires too much time. Further in work which requires special accuracy the haptoglobin type must also be estimated. In this study immunodiffusion methods could not be employed because neonates with exchange transfusion possibly had haptoglobins of several types in their circulation. The immunochemical methods based on turbidi or nephelometry (91) are rapid and they can be automatized Because modification for small sample volumes is difficult (91) these methods were not included in this study The methods based on the changes in spectrum are quick accurate even in low concentrations and modified for microsamples (102 141) Thus they are suitable for investigation of neonates.

In principle any method based on enhancement of the peroxidatic activity is suitable for the present purposes The present peroxidatic method was chosen as a routine method because we have long experience of it in our laboratory An important point is also that results are available very quickly Especially in microsamples it is also significant that hemolysis does not interfere with the method Hemolysis was revealed to have some diminishing effect on the results When hemoglobin concentration was 1000 – 1800 mg/l the result was approximately 10 per cent lower than for the same sample without hemoglobin Thus strong hemolysis occurs very seldom in routine samples. The influence of hemolysis was weaker on this method than the immunodiffusion method The immunochemical methods gave accurate results when hemoglobin concentration was low but in high concentrations the effect was very strong The immunochemical and peroxidatic methods have also been compared before and the results are similar (24) In any case the influence of hemolysis on immunochemical methods was weaker in that study than in the present study Nyman has also investigated the sensitivity of peroxidatic methods to free hemoglobin (129) Her results are similar to both of the investigations mentioned above

The present method measures plasma hemoglobin binding capacity which almost alone is attributable to haptoglobin In addition to this also hemopexin and albumin may have some hemoglobin binding capacity (66 67) Thus the present method is not specific for haptoglobin. This is apparent because »haptoglobin» was present in samples even when it was not detectable by immunochemical methods In all cord blood samples hemoglobin binding capacity was measured whereas immunochemically detectable haptoglobin was present only in 16 of 30 samples This result is similar to those in the literature (e.g 132, 133) In the present study hemoglobin binding capacity of cord blood was within the range 0 03 – 0 10 g/l

High haptoglobin concentrations of infected infants can be measured with all quick methods, because high sensitivity is not necessary for that purpose.

The stability of haptoglobin samples was investigated at +4 C. It was found out that no changes take place in a couple of days, but longer storage does have an effect on haptoglobin concentration when measured by peroxidatic method Other data are also available according to which haptoglobin is stable in a deep freezer and rather stable

in a refrigator (94) It is apparent that haptoglobin is destroyed quickest if repeated thawing and freezing takes place during the storage (94)

The sources of errors are greater when capillary samples are used. Also during the procedure a micromethod is more sensitive to errors than a macromethod. In this study the differences between micro- and macromethods were investigated by carrying out estimations of one sample with both modifications The results were similar Although the errors in sampling are greater than in the procedure the comparison of sampling was avoided because it would have made it necessary to take both capillary and venous samples from the same infant for scientific purposes only

B. PLASMA HAPTOGLOBIN CONCENTRATION IN CONTROL GROUP

As most investigations by immunochemical or peroxidatic methods show haptoglobin is present in cord blood (16 69 132 133 159) The results in this study agree with them Hemoglobin binding capacity was shown in all cord bloods with the present peroxidatic method. Haptoglobin shown by immunological methods was present only in half of the cord blood samples In healthy neonates the synthesis of haptoglobin begins only after delivery Haptoglobin concentration of cord blood was statistically significantly lower than that of neonates at the age of 1—. days. A slight increase in haptoglobin concentration still occurred during the first week, after which a decrease began. A similar decrease has been shown in earlier investigations (44 169) Haptoglobin synthesis has been shown to begin in early fetal life (57 104) Contradictory opinions have also been presented (16) It is believed that the mechanism of haptoglobin synthesis is ready in early intrauterine life, but there is no stimulus for haptoglobin production. In normal newborn infants the stimulation occurs immediately after delivery The situation seems to be identical with immunoglobulins Infection is a very strong stimulus for haptoglobin synthesis as is shown in this work. During the first days after delivery microbes invade the formerly sterile organism and, *for* example the gut receives the normal flora The acceleration of haptoglobin synthesis is perhaps connected with this phenomenon. At this moment the immunoglobulin synthesis has not begun. The decrease in haptoglobin concentrations at the end of the first week of life indicates a strong stimulus immediately after delivery and a continuous stimulus after that The half life of haptoglobin may explain the decrease (97 112) According to these results it is possible that the biological function of haptoglobin is connected with that of immunoglobulins. This problem will be investigated in later studies.

The delivery per se could also be a stimulus for haptoglobin synthesis. To clarify this problem it was investigated whether haptoglobin concentration was higher in neonates with a long delivery It was shown that there was no correlation between these factors.The methods of delivery did not have any effect on the haptoglobin concentration either

Possible hemolysis and the maturity of the neonatal liver perhaps have an effect on plasma haptoglobin concentration (16) The results in the present study indicate however that the parameters which describe these facts have no correlation to the haptoglobin concentration or to each other This could be explained by the fact that a strong stimulus occurs at this time Birth weight may however be correlated to haptoglobin concentration It is not statistically significant but indicative (Table 15) The gestation age has no effect on haptoglobin concentration. Some earlier investigations agree with these results (132 133) but some do not (16) Obviously a neonate without isoimmunization has not such a strong hemo-

lysis that it has a significant effect on haptoglobin concentration, especially because the synthesis is accelerated.

In several studies it has been shown that catheterization of the umbilical vein is a procedure during which many bacteria invade the organism despite the aseptic techniques (10 83 103 131) It is obvious that bacteremia is a strong stimulus for haptoglobin synthesis (82 171) Because it mostly occurs in the liver one can expect that bacteria which directly invade the vessels of the liver are a cause for a specially intensive stimulation of haptoglobin synthesis. Investigations on haptoglobin synthesis have revealed that glucocorticoids are necessary for this process (113 166) During the first days of life cortisol production is higher than in later life (88) During catheterization of the umbilical vein bacteria may enter the circulation and stimulate haptoglobin synthesis. When also the production of cortisol is abundant the organism has all the possibilities for intensive production of haptoglobin The results of the present study indicate that the catheterization of the umbilical vein causes such an increased production of haptoglobin that haptoglobin concentration of neonates with catheterization is significantly higher than in other neonates in the control group (Table 14) The wide variation in haptoglobin concentrations may be due to quantitative differences in invasion of bacteria.

The control group of this study consists of hospital patients who had no signs or symptoms of infection In order to learn the reliability of the values in this group haptoglobin concentrations in 21 healthy neonates were also investigated at the age of 1—2 days. The mean of the concentrations of these neonates was somewhat higher than that of hospital patients but the difference was not statistically significant. It must be noted that when determination of haptoglobin concentration is used to diagnose infection the patients are always hospitalized. The fact that the control group consists of hospital patients may have a favorable effect on the results

C. PLASMA HAPTOGLOBIN CONCENTRATION IN NEWBORN INFANTS WITH EXCHANGE TRANSFUSION

The purpose of estimation of plasma haptoglobin concentration of neonates with exchange transfusion was to investigate whether haptoglobin is a clinically useful indicator of hemolysis The results indicate that plasma haptoglobin concentration in neonates with exchange transfusion due to hyperbilirubinemia without isoimmunization is the same as in the control group. On the other hand concentration in neonates with isoimmunization is lower (Table 18) It is obvious that in those children with strong hemolysis plasma proteins with the ability to transport hemoglobin mostly haptoglobin are consumed.

This confirms that very young even premature infants have haptoglobin in their circulation. Obviously estimation of plasma haptoglobin concentration does not however give any further information on the need for exchange transfusion In all cases haptoglobin concentration is low and no clear differences from the control group are found (Table 18) ABO immunization is sometimes difficult to diagnose In those cases estimation of haptoglobin concentration may help because concentration in neonates with exchange transfusion due to hyperbilirubinemia without isoimmunization is significantly higher than that in ABO immunized newborns.

By following the decrease of haptoglobin concentration after exchange transfusion, indicative information of the strength of hemolysis can be found. This may give some signs for possible new exchange transfusions at a later date Bilirubin concentration however yields more information because the

purpose of repeated exchange transfusions especially in ABO and Rh immunized neonates is to remove bilirubin from the organism Subsequently it is more appropriate to follow the changes in bilirubin concentration than in haptoglobin concentration.

The decrease in haptoglobin concentration after exchange transfusion is identical in cases with exchange transfusion due to ABO immunization or hyperbilirubinemia without isoimmunization. The speed of the change alone varied somewhat in these groups (Figure * 4). The change related to Rh immunization was however totally different In these cases haptoglobin concentration decreases very quickly after exchange transfusion to the level before exchange transfusion. This lasted for about one day and after that concentration increased very quickly to the level immediately after exchange transfusion (Figure 3) Such a change in connection with exchange transfusion due to Rh immunization has been described earlier although the changes were slower (104 169) In these studies the changes in cases due to other indications were not followed. No definite explanation for the rapid increase of haptoglobin concentration after the exchange transfusion due to Rh immunization has been found One possibility is that hemolysis and subsequent decrease of haptoglobin concentration stimulate haptoglobin synthesis. According to earlier studies, hemolysis does not accelerate haptoglobin synthesis (123) It is, however possible that in these cases hemolysis had lasted for such a long time that increased production was consumed by increased utilization of haptoglobin. In exchange transfusion due to Rh immunization, antibodies are usually almost totally removed from the circulation and consequently hemolysis is discontinued. Because hemolysis is initially intensive the stimulating effect on the synthesis can be considered to continue even after discontinuation of hemolysis.

D PLASMA HAPTOGLOBIN CONCENTRATION IN NEWBORN INFANTS WITH INFECTION

Newborn infants with different infections are all dealt with as one group because basic phenomena in connection with infections are fairly similar for all

Haptoglobin synthesis in neonates has been studied experimentally in animals. Alekseeva & Fenina pointed out that haptoglobin synthesis was not stimulated by experimental turpentine granuloma in newborn rabbits (4) A similar study in newborn rats has also been carried out (144) The stimulating agents were turpentine and endotoxin. The results were similar in both studies It is not clear whether the differences from reactions in humans is caused by differences in the type of reaction. Another possibility is that turpentine and endotoxin were not strong enough stimulators for haptoglobin synthesis. The effect of bacterial infection on haptoglobin synthesis in newborn experimental animals has not been studied.

It has been shown that a human fetus can synthesize haptoglobin at an early stage (35 57) It is also known that infection is a strong stimulator of haptoglobin synthesis (12* 171) Consequently it can be expected that intrauterine infection causes changes in haptoglobin concentration in neonates Compared with other acute phase proteins, haptoglobin concentration is a good parameter for investigation because in normal cases haptoglobin concentration in newborn infants is low and thus even small absolute changes can be observed. The rapid increase of haptoglobin concentration in neonates after delivery indicates that synthesis also begins quickly in healthy infants Subsequently postnatal infections cause an increase in plasma haptoglobin concentration.

Unusually high haptoglobin concentrations in some neonates have previously been discussed in some studies (60 133) According to these studies, intrauterine infection was

lysis that it has a significant effect on haptoglobin concentration, especially because the synthesis is accelerated.

In several studies it has been shown that catheterization of the umbilical vein is a procedure during which many bacteria invade the organism despite the aseptic techniques (10 83 103 131) It is obvious that bacteremia is a strong stimulus for haptoglobin synthesis (92 171) Because it mostly occurs in the liver one can expect that bacteria which directly invade the vessels of the liver are a cause for a specially intensive stimulation of haptoglobin synthesis In vestigations on haptoglobin synthesis have revealed that glucocorticoids are necessary for this process (113, 168). During the first days of life cortisol production is higher than in later life (88) During catheterization of the umbilical vein bacteria may enter the circulation and stimulate haptoglobin synthesis. When also the production of cortisol is abundant the organism has all the possibilities for intensive production of haptoglobin. The results of the present study indicate that the catheterization of the umbilical vein causes such an increased production of haptoglobin that haptoglobin concentration of neonates with catheterization is significantly higher than in other neonates in the control group (Table 14) The wide variation in haptoglobin concentrations may be due to quantitative differences in invasion of bacteria

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This confirms that very young even premature infants have haptoglobin in their circulation Obviously estimation of plasma haptoglobin concentration does not, however give any further information on the need for exchange transfusion. In all cases haptoglobin concentration is low and no clear differences from the control group are found (Table 18) ABO immunization is sometimes difficult to diagnose. In these cases estimation of haptoglobin concentration may help because concentration in neonates with exchange transfusion due to hyperbilirubinemia without isoimmunization is significantly higher than that in ABO immunized newborns

By following the decrease of haptoglobin concentration after exchange transfusion indicative information of the strength of hemolysis can be found. This may give some signs for possible new exchange transfusions at a later date Bilirubin concentration however yields more information because the

Disappearance of haptoglobin from the circulation of neonates with septicaemia was investigated after beginning of treatment The half-life of haptoglobin in these cases was 5—6 days, which is somewhat longer than in healthy individuals (97 11* 1*4) This may mean that half life in infected infants is not real measure because the stimulation and accelerated synthesis are still going on. Decrease of haptoglobin concentration was so quick during treatment that it could be used as a measure of the success of treatment. The changes in plasma IgM concentrations were investigated simultaneously It was apparent that IgM concentration was pathologically high in two cases only whereas haptoglobin concentration was pathologically high in all cases except one Because of the small amounts of samples IgM concentration could not be investigated in all cases after the beginning of treatment The available results indicate, howeve that IgM concentration increases to a pathological level about one day later than that of haptoglobin The results of the septicaemia epidemic (page 35) seem to indicate that plasma haptoglobin concentration begins to increase as early as in the latent period of the infection If this is true estimation of plasma haptoglobin concentration may play a role in diagnostics of latent infections This has clinical significance especially in inhibiting spread of ward epidemics The streptococcus epidemic mentioned earlier was stopped very soon after commencing treatment in all neonates without clinical signs or symptoms of infection but with elevated haptoglobin concentration. Before treatment was started, twelve infants had fallen ill but after commencing treatment none Elevated haptoglobin concentrations in cases of latent infection may also indicate that the infants in the control group who had elevated haptoglobin concentrations in fact had a latent infection.

The increase of haptoglobin concentration in neonates with septicaemia was so intense

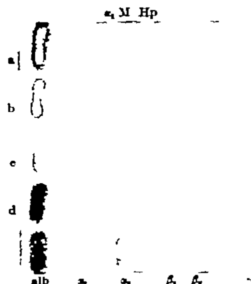


Fig Electrophoretic patterns of plasma proteins in healthy newborns and in newborns with septicaemia. Alpha$_2$-region of healthy newborns consists of alpha$_2$-macroglobulin (α_2-M) fraction only but of newborns with septicaemia two subfractions. The slower moving is haptoglobin. a — healthy newborn. b— — newborns with septicaemia.

that it was observed by even such an unspecific method as cellulose acetate electrophoresis Figure "

E. PLASMA HAPTOGLOBIN CONCENTRATION IN NEWBORN INFANTS WITH SUSPECTED INFECTION

Table "0 indicates that haptoglobin concentration of newborn infants aged 3—7 days with suspected infection is significantly higher than in the control group The difference in the total material is also statistically highly significant This result may indicate that these infants in fact had an infection. Apparently the infection never became clinical because of the defence system of the organism. High haptoglobin concentrations in infants with latent septicaemia (page 3") also point in this direction. There was no correlation in this group either between haptoglobin concentration and other parameters indicative of infections.

F SIGNIFICANCE OF ESTIMATION OF HAPTOGLOBIN CONCENTRATION IN DIAGNOSIS OF INFECTIONS IN NEONATAL PERIOD

The diagnosis of infections in the neonatal period is still difficult because the clinical pictures of these diseases vary very much. Laboratory methods in general use for example leucocyte and platelet counts and differential leucocyte count nei h r are reli able criteria for diagnosis. Plasma IgM con centration is most obviously an important criterion. Use of this method involves some difficulties because determination methods based on immunodiffusion are slow Further more one pathological laboratory parameter alone is seldom sufficient for diagnosis

The present study indicates that esti mation of plasma haptoglobin concentration in newborn infants gives valuable infor mation about infections (Tables 20 21 2_, 23 24 25) It is apparent that a neonate always synthesizes haptoglobin in connection with infections irrespective of the kind of infection Plasma haptoglobin concentration seems to increase in the initial phase of infections even as early as in the incubation period Thus greatly facilitates early diagnosis. There were however some cases of low haptoglobin concentrations despite an easily diagnosed infection (Figure 5) This phenomenon cannot be explained for the time being but it must always be kept in mind when using haptoglobin concentration in the diagnosis of infections in the neonatal period. In the control group there were as few as 11 estima ions out of 417 with clearly elevated haptoglobin concentration. In these cases the reason for high values may be a latent infection.

VII SUMMARY

The purpose of this study was to investigate whether estimation of plasma haptoglobin concentration in neonates has any significance in diagnosing infections in that period of life. Simultaneously the significance of haptoglobin and estimation of its plasma concentration were studied in connection with exchange transfusions. In order to evaluate the results, haptoglobin concentration in a control group was also estimated. In order to be able to apply the potential positive results in clinical work, a sufficiently sensitive and quick method for practical work was one of the aims of the study also.

The method employed for plasma or serum hemoglobin binding capacity was the peroxidatic method of Tarukoski (157). This method was compared directly alongside immunochemical methods and the Rivanol® precipitation method.

The control group consisted of 242 hospital patients who had no signs or symptoms of infection. The indications for hospitalization are presented in Table 4, page 20. Haptoglobin concentrations in 21 healthy neonates were also investigated. No difference between these groups was found. Haptoglobin concentrations of 30 samples of cord blood were also included.

By the method used, which measures the hemoglobin binding capacity, haptoglobin was found in small amounts in all samples of cord blood: mean ± SD = 0.07 ± 0.05 g/l (HbBC).

Haptoglobin was found by double immunodiffusion in 16 of 30 samples of cord blood. Haptoglobin concentration increased immediately after delivery and in infants aged 1—[illegible] days was as follows: mean ± SD = 0.[illegible]0±0.08 g/l, aged 3—7 days 0.24±0.14 g/l. After this concentration decreased slightly: in the age group 8—14 days it was 0.18±0.07 g/l and in the group over 14 days 0.16±0.07 g/l.

The comparison group also included 90 samples from neonates with catheterization of the umbilical vein. The plasma haptoglobin concentration of these children was statistically highly significantly higher than in other neonates of the control group. The means and standard deviations in these groups were as follows: 0.24±0.14 g/l and 0.19±0.09 g/l.

Samples taken at the beginning of exchange transfusion showed that haptoglobin concentrations in neonates with hyperbilirubinemia without isoimmunization were in the same range as the control group. When the cause of exchange transfusion was isoimmunization, plasma haptoglobin concentration was decreased. Haptoglobin concentrations (mean ± SD) in the control group and in neonates with exchange transfusion due to ABO immunization, Rh immunization or hyperbilirubinemia without isoimmunization were as follows: 0.20±0.10 g/l, 0.1[illegible]±0.11 g/l, 0.16±0.14 g/l, 0.2[illegible]±0.1[illegible] g/l respectively. The difference between haptoglobin concentrations in neonates with exchange transfusion due to hyperbilirubinemia without isoimmunization and to ABO immunization is statistically significant.

After exchange transfusion the changes in

haptoglobin concentration were followed. The results indicate that if the reason for exchange transfusion was ABO immunization or hyperbilirubinemia without isoimmunization, plasma haptoglobin concentration decreased evenly to reach the level before exchange transfusion. Half-life of exogenous haptoglobin was in these cases 4.5 days for infants with ABO immunization and 4.0 days for those with hyperbilirubemia without immunization. In the case of Rh immunization plasma haptoglobin concentration decreased quickly to the level before exchange transfusion, but after that the concentration increased very soon. The reason for this may be stimulation of haptoglobin synthesis by hemolysis. Elevated haptoglobin concentration does not normally occur because continuous hemolysis consumes haptoglobin. In this case however hemolysis is immediately discontinued by exchange transfusion and haptoglobin increases.

In connection with intrauterine infections ([illegible]9 cases) plasma haptoglobin concentration increased statistically highly significantly contrasted with the control group mean ± standard deviation 0.72 ± 0.40 g/l.

In neonates with postnatal infections (70 cases) the situation was the same: 0.99 ± 1.31 g/l. The difference from the control group was highly significant.

Plasma haptoglobin concentration in newborn infants with neonatal septicaemia ([illegible]3 cases) was 1.42 ± 1.14 g/l. The difference from the control group was highly significant.

Haptoglobin concentration was slightly elevated in neonates with suspected infection (32 cases) 0.54 ± 0.57 g/l. Even in this group the difference from the control group was statistically highly significant.

In connection with septicaemia particularly haptoglobin concentration decreases quickly after commencement of antibiotic treatment. It was also noted that haptoglobin concentration was already elevated in the incubation period of infection.

This study indicates that estimation of plasma haptoglobin concentration is a quick and usefull criterion for diagnosing infections in the neonatal period. As to the function of haptoglobin, the present study has revealed facts that indicate its connection with immunological phenomena, especially that of initial phase of infections.

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ANALYSIS OF SERIAL ECHOENCEPHALOGRAMS IN HEALTHY NEWBORN INFANTS DURING THE FIRST WEEK OF LIFE

A COMPARATIVE STUDY BY ONE AND TWO DIMENSIONAL ECHOENCEPHALOGRAPHY

BY TAPIO VALKEAKARI

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKH

ANALYSIS OF SERIAL ECHOENCEPHALOGRAMS IN HEALTHY NEWBORN INFANTS DURING THE FIRST WEEK OF LIFE

A comparative study by one and two-dimensional echoencephalography

TO MY FAMILY

ACTA PAEDIATRICA SCANDINAVICA
SUPPLEMENT 242, 1973

From the Department of Paediatrics (Head Professor Tuomas Peltonen M.D.) *University of Turku Turku, and from the Department of Paediatrics (Head* Professor Kauko Kouvalainen, M. D.) University of Oulu, Oulu, Finland

ANALYSIS OF SERIAL ECHOENCEPHALOGRAMS IN HEALTHY NEWBORN INFANTS DURING THE FIRST WEEK OF LIFE

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CONTENTS

Definitions and abreviations

DEFINTTIONS adapted from the terminology recommended by AIUM.

Mode	a method of data presentation on the oscilloscope
A mode	data presentation by using the amplitude modulation
B-mode	data presentation by using the intensity modulation
A-scan	a one-dimensional tracing registered by the A mode type of visualization
B-scan	a two-dimensional recording composed of a large number of one dimensional B-mode tracings
Absorption	energy transferred to the tissue
Artifact	any echo which does not correspond either in distance or direction to an impedance discontinuity along the indicated axis
Attenuation	loss of energy of the sound propagating through the medium
Calliper	device with curved legs used for measuring diameters
Cephalometry	measurement of distances in the skull
Dynamic range	difference in decibels between the amplitude of the largest and the smallest signal required to obtain the total scale of the display
Echoencephalogram	display obtained from the brain with reflection techniques
Gain	the ratio in decibels of echo amplitude of output to input of the electronic amplifying system
Pulse repetition rate	number of energizing pulses per second applied to the transducer
Resolution	the ability of the system to resolve closely lying structures
Depth resolution	resolution of system along the beam axis
Lateral resolution	resolution of system normal to the beam axis

ABREVIATIONS

AIUM	American Institute of Ultrasonics in Medicine	dB	decibel
		C	centigrade
BMI	brain mantle index	Hz	Hertz
CMI	cella media index	λ	wavelength
CRT	cathode ray tube	v	sound velocity
C. S F	cerebrospinal fluid	f	frequency
CTHI	contralateral temporal horn index	l	length of the near field
EVL	ear vertical line	D	diameter of the probe
HL	horizontal line	α	the angle of divergence the angle of incidence
LVI	lateral ventricle index		
PEG	pneumoencephalography pneumoencephalographic	β	the angle of refraction
		Z	acoustic impedance
P_1	temporal test point	ρ	specific density
P_2	parietal test point	I_O	intensity of the incident sound
Thru	transmission method	I_R	intensity of the reflected sound
oe	scalp oedema	I_T	intensity of the transmitted sound
		m/s	metres per second
a, b c d	distances measured in pictures and	W/cm^2	watts per square cm
e f g	used for calculation (see *Fig 7*)	N	number of subjects

I INTRODUCTION

During the last two decades the position of ultrasonic diagnostics has become established in several fields of medicine. The use of ultrasound has been especially common in neurology, ophthalmology, obstetrics, and gynecology. In neurology the attenuating effect of the skull bone in adults has limited the use of ultrasonic examination mostly to the determination of the position of the midline. In paediatric neurology it is also possible to register the sizes of the cerebral ventricles and to diagnose intracranial space-occupying lesions, cerebral atrophies and anomalies.

Several echoencephalographic studies concerning children have been published. However newborn infants are included only in some papers. Nevertheless, there are plenty of cases where a more detailed examination of the newborn brain would be useful. The diffuse neurological symptoms on one hand and the different causes of similar symptoms on the other hand make neurological diagnosis difficult in newborn infants. As regards the symptoms and signs of a newborn infant, one cannot always say whether they are caused by a neurological disorder or perhaps by completely other reasons. Mild and transitory neurologic abnormalities are a common finding during the first few days of life. These probably relate to the inevitable trauma of birth (10). The neuroradiological methods are laborious and their application in newborns is not without danger. Neither are there normal values available for newborns, because neuroradiological examinations have not been performed on healthy newborn infants (84, 102). Therefore a quick, safe and reliable method for neurological examination of the neonatal would be most helpful.

An echoencephalographic examination can safely and quickly be carried out in the newborn. Therefore it is suitable for neurological examinations during that period. A reliable evaluation of examination results requires, however, that the normal values and normal variations in the ultrasonic anatomy of the neonatal brain are known.

The applicability of the two-dimensional echoencephalography in children has been established in several papers during the last few years. The two-dimensional echotomogram makes it possible to identify the echoes more reliably than in the one-dimensional method, and thus it increases the accuracy of the examination. Against this one must set the disadvantages of the greatly increased complexity of the electronic equipment, naturally with much higher expense.

In the Department of Paediatrics, University of Turku, examinations with ultrasound were started in 1964 by Professor Tuomas Peltonen, who used it in neuropaediatric cases. The present author had the opportunity to start working in the field of ultrasonics under his guidance in 1966, first using the one-dimensional method. Two years later also the two-dimensional echoencephalography became available.

The scarcity of the normal values of echoencephalography in newborn infants gave the author a stimulus for an attempt to determine them and at the same time to study the possible effects of delivery on the anatomy of brain during the first week of life. Besides that, a comparative study between the one-dimensional and two-dimensional methods of echoencephalography was thought to be useful.

II REVIEW OF LITERATURE

A. FUNDAMENTAL PHYSICAL PROPERTIES OF ULTRASOUND

Ultrasound consists of mechanical vibrations propagated in a medium. Its frequency is above the perception of the human ear, for which the upper limit is between 16 and 20 kHz depending on age. Physically ultrasound observes the same laws of acoustics as audible sound. It cannot *propagate in a vacuum. Its capacity to penetrate* gases is also extremely limited because gases reflect almost all of the ultrasonic energy at the interfaces between them and fluids or solid substances.

Ultrasound is usually generated by the so-called piezoelectric effect. Crystals, *e. g.* quartz or barium titanate, alter their dimensions in an electric field. And vice versa, if the dimensions of the crystal are changed by intermittent pressure, registrable electrical potentials are produced.

The velocity of ultrasound in human tissues (the bones excluded) is fairly equal with its velocity in water, *i. e.* about 1 523 m/s at 37° C (227). The variations between different tissues are very slight. For *instance, in muscle* the velocity is reported to be from 1 568 to 1 585 m/s (186, 214) and in the cerebrospinal fluid (C.S.F.) 1 500 m/s (178). For the velocity in brain values from 1 515 to 1 541 m/s have been reported (108, 178, 214). *According to Willocks et al.* (228) the velocity of ultrasound in the brain of a live newborn is 1 5[illegible] m/s. The sound velocity in bone, however, is much higher. Values from 3 360 to 4 080 m/s have been described (79, 108, 186, 214).

By the laws of acoustics the wavelength (λ) depends on the velocity of sound (v) and on the frequency (f) as follows:

$$\lambda = \frac{v}{f}$$

The frequencies commonly used in neurological diagnostics are from 1 to 4 MHz, usually 2 MHz.

Near the probe the ultrasound is propagated in a parallel course forming the near field, the *legth of which (l) can be calculated using the* formula

$$l = \frac{D^2}{4\lambda}$$

where D is the diameter of the probe.

Beyond the near field the beam tends to diverge. The angle of divergence (α) depends on the frequency as follows:

$$\alpha = 1.22 \times \frac{v}{Df}$$

Thus the divergence is inversely proportional to the frequency. On the other hand, the absorption of ultrasound is approximately proportional to the frequency in all soft tissues (79). *Measurements of skull bone performed by Hueter* (93) indicate that the absorption is roughly proportional to the square of the frequency up to about 2 MHz. In brain tissue the absorption at 2 MHz is from 1.5 dB/cm (108) to 1.7 dB/cm *(214) and in skull bone 45 dB/cm (93), respectively.* With the increasing absorption the capacity of ultrasound to penetrate the tissues will decrease accordingly.

At an interface part of the ultrasound will *reflect so that the angle of incidence is equal to* the angle of reflection. The transmitted wave

continues to travel in the new medium with a speed characteristic of that medium. A refraction takes place at the interface by Snell's law

$$\frac{\sin \alpha}{\sin \beta} = \frac{v_1}{v_2}$$

where

α = the angle of incidence
β = the angle of refraction
v_1 = the velocity in medium 1
v_2 = the velocity in medium 2

The intensities of the reflected power and the transmitted power are dependent on the acoustic impedances of the two media. The acoustic impedance (Z) is

$$Z = \varrho \times v$$

where ϱ = the specific density and v = the velocity of sound.

The acoustic impedance of brain tissue is 1.56×10^5 g/cm²s, of C.S.F. 1.51×10^5 g/cm²s, of bone 6.1×10^5 g/cm²s and that of air 43 g/cm²s (79, 108).

If the beam is directed perpendicular to the interface, the intensity of the reflected power is

$$I_R = I \times \left(\frac{Z_1 - Z_2}{Z_1 - Z_2}\right)^2$$

where

I_R = the intensity of the reflected sound
I = the intensity of the incident sound
Z_1 = the acoustic impedance of medium 1
Z_2 = the acoustic impedance of medium 2

The intensity of the transmitted power (I_T) can be calculated likewise using the formula (214)

$$I_T = I \times \frac{4Z_1 \times Z_2}{(Z_1 + Z_2)}$$

It is evident that almost all the power will be reflected at an interface between tissue and air. On the other hand, only 0.03 per cent of the intensity of the incident sound will be reflected at interfaces between brain tissue and C.S.F. (181).

The choice of the characteristics of the probe depends decisively on its use. Particularly at neurological examinations in various ages several different probes are needed for obtaining the optimal result due to the attenuation in the skull bone.

B. THE BASIC PRINCIPLES AND CHARACTERISTICS OF ULTRASONIC EQUIPMENTS

The operation. In ultrasonic examinations the registration of either the transmitted wave (the transmission method) or the reflected wave (the echo method) can be used. The transmitted power can be received by using a separate probe as a receiver. In the echo method the same probe is usually functioning both as a transducer and a receiver. This is possible because of the use of short ultrasound pulses transmitted into the tissue instead of the continuous ultrasound used earlier. The pulse length is usually from 2.5 to 5 μs, and the pulse repetition rate from 200 to 400 per second. The major part of the time the probe is functioning as a receiver. Since the velocity of sound in the medium is known, the distance travelled by the sound can be calculated on the basis of the time lapse between the transmitted and the received power. The electrical potentials generated by the travelling sound can be registered on a cathode ray tube (CRT). If the potentials are visualized as vertical deflections arising from the base line, the type of registration is called A-mode. Another method to visualize the sound energy is to use the so-called B-mode where the base line is not seen on the CRT. Instead of the vertical deflections bright spots are seen on the screen. Depending on the CRT the brightness of the dots is somewhat related to the amplitude of the deflection in A-mode.

The CRT of the ultrasonic equipment used for diagnosis is usually supplied with a scale. The equipment may be calibrated so that the distances in the tissue can be read directly on the CRT. The registered echograms can be photographed on the CRT screen.

The equipment used for neurological examinations is usually supplied with the A-mode and

transmission methods. A method for obtaining ultrasound tomograms from the object has also been developed for the use of B-mode. In this case mechanical couplings or an angle computer are used to indicate on the CRT the position and the angle in space of the probe which is fixed to the end of a mechanism of the pivot arm type permitting the movement in only one plane. Simultaneously the echoes of different interfaces are also visualized on the screen as intensity modulated spots When the probe is moved, a tomogram formed from a large number of one dimensional echograms, the so-called B-scan is obtained. Depending on the movement of the probe, different names for the examination method are used e g linear scanning arc scanning, sector scanning and circular scanning The combination of the latter two is called compound scanning The tomogram can be photographed by having the shutter open during the examination. Another way is to use a storage tube, on which the tomogram can be registered several times, if needed, and photographed when the result is satisfactory

The resolution The resolution in the direction of the sound beam or the depth resolution means the shortest distance between two point targets which can be registered as distinct objects on the screen In the best case this distance is equal to one wavelength. In B-scan the resulotion may be restricted by the size of the spot, which is about 0.5 mm on a CRT of high quality and about 1 mm on a storage tube. The distance between two interfaces must thus be at least equal to the spot size in B-scan before they can be registered as distinct echo lines when the scale is 1 1 When other scales are used the depth resolution is proportional to the scale (119 121) The dynamic range of the equipment, i e the difference between the strongest and the weakest registrable echo in dB, affects both the depth resolution and the lateral resolution (120) The dynamic range of A mode equipment is about 40 dB and that of B-mode equipment about 20 dB The use of a storage tube and the photographing of the recording will decrease the dynamic range to less than 20 dB (214)

According to Wells (214) the time duration of the displayed pulse is about 1.5 2.5 and 3 wavelengths with the dynamic ranges of 10 20 and 30 dB, respectively Thus the length of a strong echo on the screen is greater than the length of a weak echo and therefore a strong echo can overlay other echoes following it on the screen. If the intensity of the received echo pulse is 30 dB the pulse amplitude rises rapidly above the treshold of visualization. If the intensity of the echo is 20 dB, the visualization of the echo will take place 0.3 wavelength later than where the position of the reflecting surface really lies. By 10 dB the echo appears about 0 8 wavelength later or if half wave demodulation is used, only 0.3 wavelength later (214) This phenomenon has significance when one is measuring the distance between two echoes, the intensities of which differ markedly from one another Oksala (161) studied the effect of amplification on the measurement of pigs lenses and suggested that the amplification of the equipment has no bearing on the results, except in cases where the echoes are very low

An echo with high intensity will be registered on the screen even if the reflecting point did not lie exactly on the axis of the ultrasonic beam. In B-scan this will cause a point target to be visualized as a line parallel with the movement of the probe, because the equipment will register the echo as if it came laways from the direction of the axis of the probe (120 159 221) For this reason the lateral resolution which depends on the beam width and beam spreading (157) is as much as ten times worse than the depth resolution (214)

In B-scan echoes from the same reflecting point can be obtained when the examination is made from different directions. The echoes will cross each other at the real place of the point examined, if the calibration of the equipment is done correctly Otherwise the point will reflect echoes at several places on the screen and the picture will be distorted (59) As the sound velocity in the skull bone is more than twice the velocity in the brain tissue, a slight distortion of

the picture can never be avoided. The distortion will still be increased by the refraction and diffraction and the variations in the attenuation of the ultrasonic field caused by the variations in the thickness of the skull bone (219 222, 224 225 226)

C. THE CLINICAL USE OF ULTRASOUND IN NEUROLOGY

The first attempts to use ultrasound in medical diagnostics were reported by Dussik in 1942 (49) His purpose was to determine the differences in the absorption of the brain by transmittance of ultrasound through the intact skull. It has, however later been proved that the differences in absorption caused by the variable thickness of the skull bone exceed the differences caused by brain (83 223) By using the pulse echo method French Wild and Neal (62) diagnosed brain tumors post mortem by applicating the probe on the surface of the brain Concerning also the pulse echo method, t was suggested that the results obtained when searching through the intact skull would be unsuitable (83 198) However Leksell using markedly lower frequency was able to obtain echoes from the midsagittal plane of the brain (134) Leksell named the method echoencephalography In his echograms he distinguished an initial echo, a bottom echo and a midline echo (134) At about the same time also Gordon found a means to register echoes from the brain through the intact skull He published his findings only some years later (73, 74 75)

Several authors have thereafter confirmed echoencephalography to be suitable for investigating the anatomy of the brain (22 60 103 104 107 108, 114 115 138 139 140 170 180 190, 208) In all the studies mentioned above the echoes were visualized by using the A mode even if the Japanese authors were already making attempts to introduce the two-dimensional B-scanning (114 188)

A-scan echoencephalography

In all A-scan examinations through the intact skull the echo deflections already described by Leksell (134) can be observed the initial echo and the bottom echo, also called the end echo. In addition, echoes from several interfaces of the brain may be obtained depending on the test point used for examination. The most commonly used test point lies on the temporal area just above the external auditive canal.

The initial echo

The initial echo is normally visualized on the left side of the oscilloscope screen. It consists of an echo complex which includes deflections caused by the vibrations of the probe and echoes from the different interfaces of the tissues of the head wall. The length of the initial echo depends on the thickness of the head wall, the transmitter power and the sensitivity of the receiver (178) Brown (27) has pointed out that when one is using an equipment with adequate near field resolution the echo of the ipsilateral inner table of the skull can be identified in the initial echo complex.

The end echo

The end echo will be visualized on the right side of the screen as one or several echo deflections. Smyth (184) distinguished three or four single deflections in the end echo complex suggesting that the first deflection originates at the interface of the brain and meninges, the following two at the inner and outer tables of the temporal bone and the final deflection at the interface between skin and air Schiefer *et al.* (178) have pointed out that when the frequency of 2 MHz is used the echo of dura cannot be separated from the echo of the inner table of skull bone. Oberschulte Beckman and Otto (158) suggested on the basis of their study on cadavers that the dura itself can give n echo complex equal to the normal end echo complex

To determine in the end echo complex the o which originates at the skin/air in

The temporal horn of the lateral ventricle The registration of the temporal horn echo has been used widely for determining the thickness of the cerebral cortex, the so-called brain mantle in the temporal area (5 16, 22 72, 80 90 91 100 106 111 127 128 152, 155 177 199 201 202, 229 230) According to ter Braak *et al* (22) the echo of the opposite temporal horn is situated at 3/4 distance between the place of the probe and the opposite inner wall of the skull The source of the echo has been identified by filling the temporal horn with air in which case the intensity of the echo will rise markedly Jefferson and Hill (105) recorded echoes from the ipsilateral temporal horn. They also identified the source of this echo by using air

Schiefer *et al* (177) described in 1965 an echoencephalographic brain mantle index (BMI) using the position of the lateral wall of the temporal horn The index was calculated as the relation between the distances from the midline echo to the end echo and from the lateral wall of the temporal horn to the end echo. The authors reported 2.0 to 2.2 to be the normal range of values. Dill (38) has calculated the index as the reciprocal value, and she reported 0.5 ± 0.05 to be normal values. The horizontal diameter of the temporal horn has been reported by Dill (38) to be 2 mm and by Jacobs *et al.* (100) from 2.5 to 4 mm during the first year

The echoencephalographic brain mantle index values have been controlled by using pneumoencephalographic (PEG) studies. General agreement has been reached in almost all cases (38 87 111 178 197)

The body of the lateral ventricle Besides the temporal horns the lateral walls of the bodies of the lateral ventricles have most commonly been visualized by ultrasound when the size of the ventricular system has been estimated (7 16, 22, 69 71 72, 90 110 111 126 128, 131 136, 145 154 167 181 183 195 196 197 199 201 215 216) The lateral ventricles can be registered from the test point about 4—5 cm above the external auditive canal (9 217) According to Brown (27) the lateral ventricle echoes are single or double echoes at equal distances from the midline echo which originates from the septum pellucidum.

Echoes of the bodies of the lateral ventricles have been indentified by injecting air into the ventricles (22, 60) If a needle is inserted at right angles to the ultrasonic beam into the source of the supposed lateral ventricle echo in the brain of a cadaver a stronger echo has been seen than before The location of the needle can be determined when the brain is sectioned (51 78 140)

To estimate the size of the lateral ventricles several authors have suggested different grounds for calculations. Lithander (139) reported that in none of 30 healthy newborns the distance from the midsagittal plane of the skull to the lateral wall of the ventricle exceeded 25 mm. Dill (38) gave values from 8 to 15 mm for infants less than 12 months of age. Umbach and Kley (197) suggested that the diameter of one lateral ventricle in a normal small child makes less than 25 per cent of the diameter of one cerebral hemisphere. Sjögren presented in 1965 the so-called lateral ventricle index (LVI) The index is calculated as the quotient of the combined transverse diameter of the lateral ventricles and the diameter of the head. Normally this quotient should not exceed 1.3 (180) The newborn subjects had the highest values for lateral ventricle index, *i.e.* 0.30 ± 0.03 A slight decrease of the index took place during the first year of life (180) Kruggman has also reported corresponding values for the lateral ventricle index (125) Values presented by Dill (38) too, were higher in infants less than 12 months old than they were in older children. Brahme and Trägårdh (23) suggested, however that the lateral ventricle index, calculated by them as the relation between the width of one lateral ventricle and half of the diameter of the skull was low in the newborn (maximum 0 18) and increased up to the age of one year

Kazner and Hopman (111) presented the so-called cella-media index (CMI) which is calculated as the relation between the biparietal diameter as measured by calliper and the combined transverse diameter of the bodies of the lateral ventricles. Thus the CMI corre

sponds to the reciprocal LVI The normal values are higher than 4 1 corresponding to the LVI values of 0.24 or less (111)

According to Mostafawy (154) post-traumatic, transitory dilatation of the ventricular system can be detected by the determination of the lateral ventricle index and by the measurement of the width of the third ventricle

The reliability of the determination by ultrasound of the diameter of the bodies of the lateral ventricles has been proven by PEG studies (38 45 61 69 85 87 122, 150 154 179 183 197 215, 217) On the other hand, Hunter *et al* (94) have postulated on the basis of their PEG investigations that the width of the body of the lateral ventricle is the most reliable single indicator of the size of the lateral ventricle.

Other lateral echoes

Also other interfaces between brain tissue and C. S. F produce echoes. Echoes from the Sylvian fissure can be detected by horizontal sounding from the temporal test point (78, 104 140 176, 190) Lithander (140) identified the Sylvian fissure echo by inserting needles in the brain specimens of cadavers. Uematsu and Walker (193) suggested that in children below the age of two the normal proportion of th distance between the Sylvian fissure and the skull to the transverse bitemporal diameter is about 20 per cent and in premature babies between 16 and 20 per cent while in adults and in children over two years of age t is a l ttle less than 25 per cent. Bergström *et al* (17) ha e presented on the basis of their angiographic studies that the distance from the midline to the middle cerebral artery lying in the Sylvian fissure, is about 61 per cent of half of the inner cranial diameter in children aged less than five.

Alvisi has described echoes from circumpeduncular cistern or the surrounding structures. The probe is n this case placed close to the upper root of the ear somewhat lower than when examining th temporal horns (6)

Reflections from interfaces between white and gray matter in cadaver brain have been described by Lithander (140) Dreese and Netsky (46) and Grossman (78) Especially in children with thin skull bones small echoes can be registered from the brain parenchyma. Fluid-filled cavities do not produce such echoes, which is an important differential diagnostic fact (180)

B-scan echoencephalography

The first two-dimensional echotomograms through the ntact skull were described by Japanese authors (114 115, 188) The first references in Europe about the possibility to use B-mode technique for the examination of brain through the skull are from the year 1961 (22, 156 190) In 1963 de Vlieger *et al* (209) reported their results from the examination of normal subjects and of patients with hydrocephalus by the B-scan method. Thereafter numerous authors have described results obtained by this two-dimensional method of echoencephalography (1 2 3 4 8, 24 52 53 64 66 67 77 98, 109 118, 147 148, 151 159 163, 173 174 199 200 203 206 207 211)

A mode and B-mode differ from each other in the visualizing technique since different methods of modulation are used. Therefore, the same restrictions concern both methods, i e registrable echoes can be received only from those interfaces which are parallel with the skull bone and thus perpendicular to the ultrasonic beam (79 143, 219) Attempts should be made to perform the examinations by using those planes in which the position of the reflecting surfaces is most useful for recording The planes most commonly used are the so-called modified horizontal plane (37 44 47) and the standard coronal plan (26 204) In addition, other planes parallel with the ones mentioned above have been used (6 143) The best results in B-scan have been achieved in infants and in children whose skull is relative thin (37 109 142 143 ?01 204)

The initial echo

In B-scan echoencephalography the initial echo complex is represented by a smooth dense

white line 3 to 5 mm thick. This line is an artifact which is created by the display (in the first few mm of the trace) of the electrical driving impulses and the subsequent vibration of the transducer. The outer margin of this artifact corresponds to the surface of the scalp (68).

The end echo

In B-scan echoencephalography the end echo is usually not clearly definable, and it cannot therefore be used for measurements (143). Examinations from both sides of the skull are thus necessary for determining accurately the theoretical midline position (68, 92).

The midline echo

In B-scan the midline echo can be registered as echo lines from different parts of the mid structures of the brain (92, 143, 209). Echoes from well-defined interfaces of midline structures are obtained when scanning infants and young children. By this method the midline is visualized over an extremely large area both in the horizontal and the coronal planes (92). Scans done in a given plane are the equivalent of innumerable one-dimensional midline determinations. Therefore also local shifts of the mid line may easily be recognized in B-scan (68).

In horizontal B-scans the midline echo is often seen to be partly double-walled with a space in between. These interfaces probably represent the walls of the third ventricle and the intervening space shows its cavity (68, 92). The distance of the walls can be measured accurately unless the ventricle is very narrow, in which case it may be difficult to differentiate it from the septum pellucidum (143). Alvisi *et al.* (6) have pointed out that the walls of the third ventricle are hard to separate in normal cases.

Single interfaces in the midline result not only from the septum pellucidum but also from the cerebral falx. Double-walled echo lines may also be produced by the interhemispheric fissure or the cavum septi pellucidi (92).

The lateral ventricles

From the lateral ventricles echoes have been registered in the horizontal plane from the frontal horns, temporal horns, trigonum and in higher horizontal planes also from the lateral walls of the bodies of the ventricles (6, 79, 143, 189, 205, 209). In coronal scans the temporal horns and the lateral walls of bodies can be registered (143, 204, 205). Even if the lateral ventricles are not visualized as voids in patients shown to have normal-sized ventricles, strongly reflecting interfaces, parallel with the midline are, however, visualized in both horizontal and coronal scans (68). These landmarks are sufficient to indicate a normal ventricular system or to provide sufficient information for revealing the presence of diffuse or local dilatation and distortion of the ventricles (143).

The temporal horn of the lateral ventricle. The brain mantle index (BMI) cannot be calculated in B-scan as accurately as in A-scan, because the end echo is not clearly definable. Lombroso *et al.* (143) used for the same purpose a ratio between the distance from the initial echo to the lateral wall of the trigone temporal horn complex and the head diameter measured externally with callipers. The value of the index described above has been found to fall close to one fourth of the head diameter but it may fall between one third and one fifth in normal infants and children.

The body of the lateral ventricle. The lateral walls of the bodies of the lateral ventricles appear normally as short echo lines parallel with the midline (143, 187, 201, 213). The average value for the transverse diameter of the body of the lateral ventricle in newborns and infants up to 12 months has been reported to be 15 to 18 mm (143).

Abnormal findings

In case of malformations there may be extra echoes from the walls of a cyst in brain parenchyma. The cyst of septum pellucidum will produce two distinct echoes above the third ventricle (92). There can also be malformations

in which some of the normal echoes are missing In cases of monoventriculia the midline echo cannot be visualized. The malformations are easier to record in B-scan (3 92 199) but they can also be found in A-scan as described by several authors (12, 71 183 229)

B-scan versus x-ray

On the basis of neuroradiological control studies it has been concluded that the position of the midline structures can be determined correctly by B-scan in 95 per cent of cases (144) The measurements of the lateral ventricles using two-dimensional echoencephalography are consistent with the corresponding PEG findings (6 142 207 213)

B-scan versus A-scan

In theory all landmarks which can be visualized in the two-dimensional ultrasonic examination can also be detected by the one-dimensional method and vice versa. The two-dimensional method gives the possibility of showing several landmarks simultaneously in a permanent picture. Also artifacts are more easily detected in B-scan than in A-scan (15 142) The B-scan method is considered to be difficult or unsuitable for the examination of a restless patient in whom the A-scan examination is still possible to perform (109 200)

B-scan increases accuracy and makes the identification of the midline easier than in A-scan (68, 149) The estimation of the ventricular system is better with B-scan than in A-scan because the walls of the ventricles are easier to recognize (209) Valkeakari (199 201) used combined A-scan and B-scan echoencephalography as a screening method in neuropaediatric patients and reported a larger amount of correctly diagnosed cases in B-scan. Kazner (109) suggested combined simultaneous A-scan and B-scan echoencephalography as an important additional investigation to be used as a screening test in children and as a follow-up method in patients having had shunt operations.

D ULTRASONIC FOETAL CEPHALOMETRY

Measurements of the biparietal diameter of the foetal skull by ultrasound were first described by Donald and Brown in 1961 (42) The measurement is carried out by determining the distance from the outside of the proximal skull surface to the inside of the distal skull surface. According to Willocks *et al.* (228) the opposing skull margins will produce simultaneous echoes of maximum amplitude only when the beam axis lies along either the occipitofrontal or the biparietal diameter The foetal biparietal diameter is usually more or less perpendicular to the anterior surface of the maternal abdomen, and it is therefore more easily accessible than the occipitofrontal diameter The latter is also much larger than the biparietal diameter to be confused with it (228)

When the foetal biparietal diameter is examined, the visualization of the midline echo between the echoes of the skull bones is supposed to prove that the diameter of the head will be measured exactly perpendicular to the mid sagittal plan of the skull (33, 86, 193) Comparative measurements in neonates showed that there was less variation when the midline echo was used as a third reference point than if it was not used This was so in spite of the fact that frequently a higher gain setting had to be used to obtain the midline echo in foetus. Kohorn also demonstrated that at an examination of the bitemporal diameter the lateral ventricles usually lie on this axis. Therefore a ventricular echo may be seen in the foetal brain but usually not simultaneously on both sides. These findings raise the possibility of having four or five points of reference in determining the biparietal diameter (116)

To improve the results of foetal cephalometry a combination of A-scan and B-scan methods has been used (20 29 33 34 86 124 165) The orientation of the foetal head has first been determined by using B-scan and then the biparietal diameter has been measured by A-scan or by both methods. Results by the pure B-scan

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To improve the results of foetal cephalometry a combination of A-scan and B-scan methods has been used (20, 29, 33, 34, 86, 124, 165). The orientation of the foetal head has first been determined by using B-scan and then the biparietal diameter has been measured by A-scan or by both methods. Results by the pure B-scan

technique have also been reported (36, 95 172). In B-scan the midline of the foetal brain can be registered from a large area, which makes the measurements reliable (33 36 95 172). Weill *et al.* (212) have registered both the midline echo and also the lateral ventricle echoes in utero in B-scan.

The birth weight of the baby has been correlated with the biparietal diameter of the foetus by several authors. Willocks *et al.* (228) suggested that if the biparietal diameter is 8.5 cm or more the baby is unlikely to weigh less than four pounds, and if the diameter is 9 0 cm or more, the expected birth weigh is five pounds or over. According to Kratochwil (123) the biparietal diameter of 8.5 cm will fairly accurately predict a birth weight of more than 2 000 g and the diameter of 9 0 cm a birth weight of more than 2 500 g. The biparietal diameter of 8.5 cm will indicate a birth weight of 2 500 g or more in 96 per cent of cases according to Koborn (116) in 91 per cent according to Taylor *et al.* (191) or in nearly 100 per cent as presented by Pystynen *et al.* (168, 169). Ojala *et al.* (160) pointed out that with a confidence of 97.5 per cent in normal pregnancies the foetus can be said to weigh over 2 500 g when the biparietal diameter is not less than 82 mm. According to Piironen and Manninen (165 166) the birth weight will be 2 500 g or more in 7[illegible].8 per cent of cases when the biparietal diameter is between 8.1 and 8.5 cm. The regression equations between birth weight and the biparietal diameter as presented by several authors are shown in *Table I*.

The height at birth was correlated with the biparietal diameter of the foetus by Kratochwil (123). He suggested that if the biparietal diameter was more than 9 0 cm, the height at birth was 50 cm or more in [illegible]1 3 per cent of cases. According to Pystynen *et al.* (169) when the biparietal diameter exceeded [illegible]0 cm, more than half of the children were over 50 cm high. In the series of Puroinen and Manninen (165) the height at birth was 50 cm or more in 68 5 per cent if the biparietal diameter was from 9 1 to 9.5 cm. In the same group the [illegible] of the *head* was at least 34 cm in 88 3 per cent.

Table I. The regression equation between birth weight (y) and biparietal diameter (x) by several authors

The weights are given in grammes except Willocks *et al.* in ounces. The biparietal diameters are in cm except Ojala *et al.* in mm. The equation of Kratochwil is estimated on the basis of a figure in the paper

Willocks *et al.* (228)	y = 30 x — 177
Thompson (19[illegible])	y = 1060 x — 65[illegible]5
Kratochwil (123)	y = 900 x — 5200
Hellman *et al.* (86)	y = [illegible]2.2 x — 39[illegible]3.8
Koborn (116)	y = 613 x — 2599
Sabbagha *et al.* (17[illegible])	y = 953.10 x — 54[illegible]0.96
Cohen (36)	y = 953.3 x — 5341.8
Pystynen *et al.* (169)	y = [illegible]000 x — 41225
Ojala *et al.* (160)	y = 11660 — [illegible]4838 —
Puroinen *et al.* (165)	y = 696.3 x — [illegible]43

The reliability of cephalometry has been most often estimated by *comparing the results of* measurements with the *calliper* measurements performed postnatally usually during the first 24 hours after delivery. Donald and Brown (42) suggested that an error of more than 2 mm as found by calliper measurements after delivery can be regarded as a bad result. Anderson *et al.* (11) noticed an average error of 1.9 mm between the foetal biparietal diameter and the postnatal calliper value. They explained that the following factors contribute to the discrepancy: 1) measuring of the biparietal diameter to the inner surface of the skull instead of the outer surface, 2) moulding of the head during the birth and scalp oedema, 3) observer-to-observer variation in measurements made by the calliper. In the series of Kratochwil (123) the corresponding error was more than 2 mm in 8.2 per cent of cases. According to Koborn (116) the mean of the absolute differences was 2.5 mm. However in 15.5 per cent the difference was more than 4 mm. To avoid the influence of the moulding of the head Campbell (33) studied infants delivered by the Caesarean section. The average error was 0.8 mm. Scher (1 5) investigated infants delivered in breech presentation, and the difference stayed within the limit of 4 mm in 9[illegible] per cent. The calliper values were more often higher than the values obtained by ultrasound.

Hellman *et al.* (86) used combined A-scan and B-scan foetal cephalometry. They suggested that the absolute mean difference as compared to the postnatal calliper values was 1.8 mm for A-scan and 2.5 mm for B-scan. The mean of the A-scan measurements was about 2 mm larger than that of B-scan. Sabbagha (171) demonstrated that the closest correlation between prenatal ultrasonic and postnatal calliper measurements is obtained, when nonpersistent B-scan and electronic callipers are integrated into the procedure of ultrasonic cephalometry.

When comparing the *intrauterine* and the *postnatal ultrasonic* measurements Scher (173) observed that the difference was within the limit of 2 mm in 60 per cent. Pystynen *et al.* (169) suggested that in 90 per cent the difference was at the most 3 mm if the postnatal measurement was carried out within one day from the delivery. Piironen and Manninen (165, 166) discovered the difference to be at the most 3 mm in 88 per cent when the postnatal ultrasonic measurement was performed during the first day of life. In 67.6 per cent the first day value was lower than the intrauterine value in the entire series. The corresponding percentage for infants delivered by the Caesarean section was 60.

A comparison between the *ultrasonic* and *calliper* measurements of the *neonatal head* was made by Willocks *et al.* (228). In 73.5 per cent of cases the error was 1 mm or less. Scher (173) suggested that the corresponding difference was at the most 2 mm in 90 per cent. The calliper values were commonly higher than the ultrasonic ones. Campbell (35) compared his own results of the differences between the intrauterine ultrasonic and the postnatal calliper measurements with the ones that Willocks *et al.* (228) reported on the differences between the measurement performed postnatally by ultrasound and by calliper. The difference in the distribution of the discrepancies was not statistically significant.

E. THE POSSIBLE HARMFUL EFFECTS OF DIAGNOSTIC ULTRASOUND

Ultrasound is known to destroy tissue if the intensity is sufficient. The damage of the tissue may occur by a thermal effect of ultrasound or by cavitation. At lower intensities and in long time durations of exposure the lesion is produced by a thermal mechanism. At the highest intensities and shortest time durations, cavitation is believed to be the mechanism of damage (63). The tissue destruction threshold for continuous sound lies at 2.5 W/cm² for 5 minutes, according to Barth and Bulow (14). It is to be expected that a pain reaction appears at a dose lower than the dose needed for tissue damage. When pulsed ultrasound is used the mean intensity does not exceed 5 mW/cm². No observable damage of tissue has been described in normal use of pulsed diagnostic ultrasound (43, 185, 186). Falus *et al.* (54) have reported a clinical follow-up study of 117 children who had been investigated by ultrasound in utero. No malformations were found to be caused by the ultrasonic examination and the development of the children was normal. Jeppson (108) has suggested that, due to the thermal effect of ultrasound, the temperature could rise by 0.1 °C during a three minute examination if no transport of heat takes place. According to Sjögren (181), the ultrasonic echo examination method is safe even in infants although infantile tissue is more vulnerable than the tissue of adults. Kohorn *et al.* (117) examined 20 normal babies during the first three days of life with combined electroencephalography and echoencephalography. The sonic energy did not alter the cerebral electrical activity in any way.

extraction or forceps There were 46 single deliveries one infant was one of twins and in addition there were two pairs of twins.

The mean duration of the first stage of delivery was 7 hrs 19 min ± 3 hrs 15 min for primiparae with a range from 3 hrs 30 min to 16 hrs 25 min and 7 hrs 23 min ± 4 hrs 53 min for multiparae with a range from 40 min to 20 hrs 30 min The mean duration of the second stage was 12.9 ± 6 0 min (range 5—20 min) for primiparae and 7.2 ± 3.5 min (range 2—15 min) for multiparae ($p < 0.001$)

V METHODS

A. THE EQUIPMENT

The equipment used in this study was Porta scan MDU-661 BU manufactured by Picker X-ray Corp. Four presentation methods are possible A Mode Thru-Transmission, M Mode (Time motion) and Compound B-Mode Scanning M Mode was not used in this study The equipment is supplied with a storage oscilloscope (Tektronix Inc. Type 564) which has a 8 cm × 10 cm viewing area divided into an upper and lower storage screen of 4 cm × 10 cm. Each screen has its own operating and erase circuit for storage operation. There are two standard transducers of 2.0 MHz. The transducers are made of barium titanate and they have a diameter of 13 mm with a near field of 56.3 mm and a divergence angle of 4.0 The pulse repetition rate is 400 pulses per second and the duration of the pulse 1.8—2.0 μs. The same transducer also functions as a receiver except when the transmission method is used. The sensitivity is controlled by the setting of the gain control, which is not calibrated n decibels in the equipment used in the present study There are also controls for reducing the near surface echo deflections and for compensating the attenuation by amplifying the deep structure

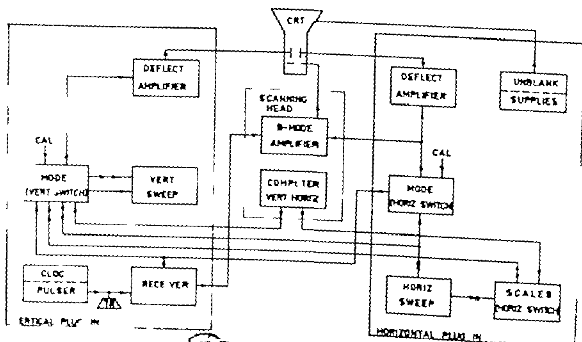


Fig. 1 Block diagram of the equipment ... the study

echo deflections more than the echoes from the near structures.

For compound B-scan operations the equipment is supplied with a hand-operated scanning mechanism of the pivot arm type. The arm has three jointed segments with the transducer at the end. Electrical measurements are made at each joint in the arm by specially manufactured data potentiometers simultaneously and continuously indicating the position and angle of the transducer in space. The entire mechanism may also be rotated about the axis of its plane of motion so that cross sections may be made at a variety of angles.

The agent of the manufacturer had taken care of the calibration procedure. The equipment was calibrated for *sound velocity in water at 25 C.* It is possible to choose the scale on the screen between 1 1 and 1.2 in A scan. For B-scan only the scale 1.2 is available. The equipment is supplied with a Polaroid-Land camera for photographing the oscilloscope screen in real size. The block diagram of the equipment is presented in *Fig 1*

B THE PRACTICAL PERFORMANCE OF THE STUDY

The infants were examined seven times during the first week of life at 3 6 12, and 24 hours, and 2 4 and 6 days with both A-scan and B-scan methods. The A-scan and B-scan examinations were performed successively so that the interval between them was 15 minutes at the most. The scale of 1·2 was used in both A-scan and B-scan examinations. The infants were lying *in supine position on the examination* table. Sonogel[R] was used as contact medium. No sedation was used for the subjects.

The A-scan examination was started by determining the theoretical position of the mid

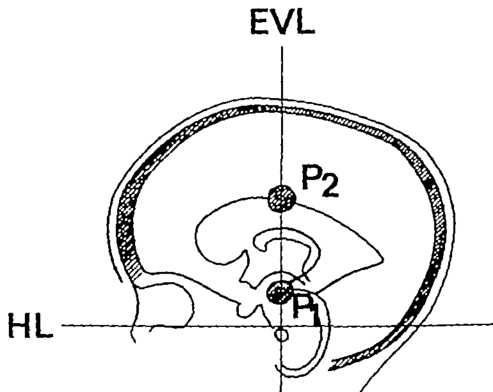


Fig 2. The position of test points in the present study P_1 = the temporal point, P = the parietal point. HL = the horizontal line EVL = the ear vertical line. (Adapted from West (217))

line by the transmission method. The contralateral temporal horn echoes were registered on both sides from test point (P_1) *(Fig 2)* just above the external auditive canal (178) at the ear vertical line (EVL) situating perpendicular to the horizontal line (HL) which connects the margo infraorbitalis and the external audi tive canal (217) The following facts were used for visualizing and identifying the temporal horn echoes in A-scan The concave curvature of the external wall of the contralateral temporal horn produces an echo deflection which is often accompanied by an other echo from the internal wall of the temporal horn thus forming a double echo (38, 100 179) The echo of the contralateral temporal horn is situated at 3/4 distance between the place of the probe and the opposite inner wall of the skull (22)

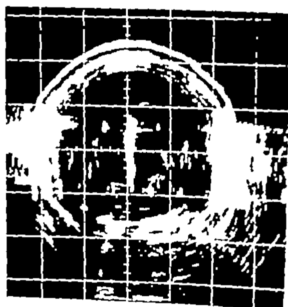


Fig 4 The coronal B-scan scanned around ... along the ear vertical lines. The reverbe... covering the leading edges of the ...

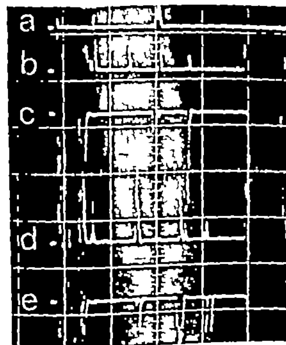


Fig 3. The A-scan registrations photographed on the same picture The order of the echoencephalograms from the top) the midline control by the transmission met hod, b) the midline echo and the body echoes of the lateral ventricles on the righ -to-left tracing,) the midline echo nd the body echo of the contralateral entricle on the left-to-righ tracing, d the righ -to-left tracing showing the temporal horn echoes as the last echoes before the end echo,) the same as d) on the left-to-right tracing, the echoes on both sides of he middle of the screen obviously originate in the circumpeduncular cisterns.

The lateral walls of the bodies ... ventricles were registered from ... on both sides at the ear vertica... em above the horizontal line ... *(Fig 2)* Single or double echoes lying ... from the midline were searc... tempts were made to visualize ... contralateral body as accura... both sides as its position wa... ing the width of the bodies ... les (181 217) The ed ... scanning with the probe ... P until representative ... screen.

The echoencephalogra... on the same plate by ... camera. The order ... picture *(Fig 3)* was ... the top a) the mid... the lateral ventricle... the same on left-to-r... horn on right-to-le... left-to-right tracing ... registered from the ... down in the picture ...

The B-scan ex...

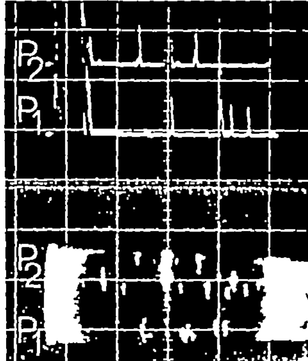


Fig. 5. The A-scan tracings examined at test points P and P on the upper screen correlated with the corresponding coronal B-scan along the EVI between P and P on the lower screen.

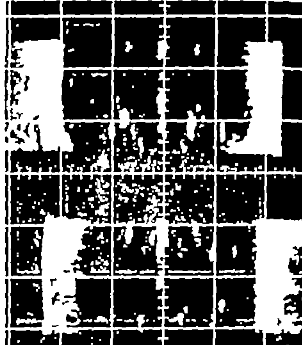


Fig. 6. The B-scans as registered during the study. The right coronal scan on the upper screen, and the left coronal scan on the lower screen.

the coronal plane along the ear vertical line on both sides using the contact-compound-scanning method. The coronal plane in B-scan goes through both test points P_1 and P_2 on each side and allows therefore a comparison with A-scan tracings. In this study the scanning was not performed around the vertex from one side to the other but only on each side between test points P_1 and P_2. This was made to avoid the distortion of the picture due to the different sound velocity in the skull bone as compared to the velocity in the brain tissue. However no information needed for comparison between A-scan and B-scan recordings was lost. In *Fig. 4* a B-scan picture scanned around the vertex in the coronal plane is shown for comparison with *Fig. 5* presenting the coronal scan as used in the present study and the corresponding A-scan tracings. (Registering the diameter of the third ventricle was not included in this study because it is difficult in normal cases to separate the individual echoes of the two walls of the third ventricle in B-scan. The usual finding is a single echoline of variable thickness as pointed out by Alvin (6)). The right coronal scan was registered on the upper storage screen and the left coronal scan on the lower storage screen of the oscilloscope. The scans from both sides were then photographed simultaneously in same picture *(Fig. 6)*.

To be sure that the A-scan and B-scan examinations were performed in the same plane the scanning arm of the B-scan equipment was used also when registering the A-scan tracings. The examination took about 5—10 minutes for the A-scan examination and equally long for the B-scan examination.

C. MEASUREMENTS

The measurements in the pictures were carried out by means of a mechanic's calliper with a tolerance of 0.1 mm. In A-scan the distances on the tracings were measured from the leading edge of the first deflection of the initial echo to

the leading edge of the echo deflection of the corresponding interface. These echoes were the midline echo the echo of the body of the contralateral lateral ventricle, the contralateral temporal horn echo and the end echo. The distance between the transducer and the receiver deflections registered by the transmission method was also measured in the same way on the tracing The distances measured in the p ctures and their symbols are shown in *Fig 7*

The measurements in B-scan pictures were carried out as in A-scan. The distances were measured from the leading edge of the initial complex to the nearest border of the echo in question (76) In A-scan the identification of the echoes was done when examining the infant while in B-scan the definite identification took place on the basis of the pictures *(Fig 6)*

The midline echo in B-scan was registered as a long strong echo line in the middl of th scan between the initial echo complex and the end echo complex.

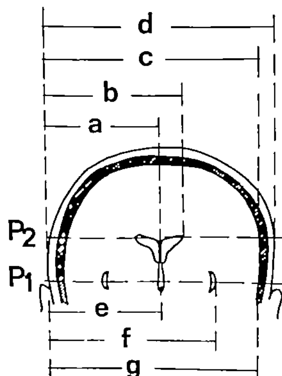


Fig 7 The distances as measured in the pictures and used for he calculations.

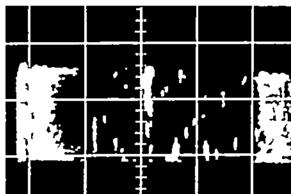


Fig 8 A coronal B-scan showing the triangular form of the cross-section of the body of the lateral ventricle nd several echoes on both sides of the midline echo.

The temporal horn echo was identified as a pair of short echo lines in the middle between the midline echo and the end echo in the lower part of the B-scan, recorded upwards and beginning just above the external auditive canal. The echo of the lateral wall of the contralateral temporal horn was used for measurements.

The echoes from the bodies of the lateral ventricles were identified as symmetrical echoes beside the midline echo, registered about 4—5 cm above the horizontal line. The echo from the ipsilateral side could not always be visualized in B-scan. However the echo from the contralater al ventricle was visualized in its normal place even if the echo from the ipsilateral ventricle was missing The contralateral body echo was used for measurements. Only in one subject none of the echoes of the bodies of the lateral ventricles could be visualized in B-scan.

If several echoes were obtained on the contra lateral half near one another the most lateral echo was used for measurements, because it corresponds to the maximal width of the body of the lateral ventricle, the other echoes being due to the width of the ultrasonic beam in those parts of the ventricular wall which lie at a shorter distance from the probe (6 27 61) A typical case showing several echoes in B-scan is seen in *Fig 8*.

When distances to the end echo were measur ed, eventual small echo deflections just before

the end echo were not taken into account. In B-scan the distance to the end echo was measured as accurately as it was possible considering the inaccuracy of the end echo.

A total of 8 921 measurements were carried out in 714 pictures. Simultaneously with the measurements of the distances, recordings with extra echo patterns and with missing echoes were looked for to detect possible malformations.

D CALCULATIONS

As the trace on the oscilloscope screen is situated somewhat deeper than the scale markings, a slight error due to parallax was observed when photographing the tracings. The error was determined by photographing straight vertical lines situating just behind the scale markings *(Fig 9)* A correction coefficient was calculated on the basis of the differences between the vertical lines and the corresponding scale markings. For the scale 1:2 used during the whole study a correction coefficient of 2.094 was obtained to convert the distances in the picture to millimetres in natural size.

The diameter of the head. The distances between the initial echo and the midline echo measured from both sides were added to get the diameter of the head at test points P_1 and P_2 in both A-scan and B-scan. The diameters in A-scan



Fig 9 Determination of the correction coefficient allowing for differences in scale and parallax.

and B-scan were compared with one another and with the diameter obtained by the transmission method at test point P_2. The values obtained at the various tests during the first week of life were compared with one another in each method. In A-scan head diameter values at test points P_1 and P_2 were also calculated excluding the oedema of the scalp (see below). The linear regression equations between the head diameter in A-scan at test point P_2 at the age of three hours with the scalp oedema excluded and the birth weight, height at birth and head circumference were calculated The Pearsonian correlation coefficient was also calculated between the respective values

The oedema of the scalp The oedema of the scalp or an extracranial haematoma increases the distance between the initial echo and the end echo when the examination is made from the side with the oedema compared to the corresponding distance measured from the opposite side (35 39 56) The difference between the distances from the initial echo to the end echo on the right-to-left and left-to-right recordings gives the oedema of the scalp The assumption was made that the oedema occurred only on one side of the head. The thickness of the scalp oedema was calculated at the ages of 3 hours, 24 hours, and 6 days in A-scan at test points P_1 and P_2.

The head wall. The thickness of the head wall on the side without scalp oedema was calculated as the difference between the diameter of the head and the distance from the initial echo to the end echo measured from the side of the scalp oedema, i. e by using the formula

$$(a_{dx} + a_{sin}) - c \text{ at } P_2 \text{ and}$$

$$(e_{dx} + e_{sin}) - g \text{ at } P_1 \quad (Fig\ 7)$$

The thickness of the head wall was calculated at the seven testing moments of the study at test points P_1 and P_2 both in A-scan and in B-scan and the means of the seven values were compared with one another

The superficial structure index (181) was calculated as a ratio between the head wall thickness and the diameter of the head

The position of the midline To avoid the effect of the scalp oedema on the determination of the theoretical position of the midline, the difference between the distances from the midline echo to the end echo on right-to-left and left-to-right tracings was calculated. Half of this difference indicates the amount of the midline shift (27 187)

$$\text{Midline shift at } P_1 = \frac{(g_{dx} - c_{dx}) - (g_{sin} - c_{sin})}{2}$$

$$\text{Midline shift at } P_2 = \frac{(c_{dx} - a_{dx}) - (c_{sin} - a_{sin})}{2}$$

(Fig 7)

If the formula gives a positive value, there is a shift to the right. A negative value indicates a shift to the left.

The above calculations were performed only in A-scan, because the inaccuracy of the end echo in B-scan makes the method unsuitable for two-dimensional echoencephalography The calculations in B-scan were made supposing that the scalp oedema in B-scan was equal to that in A-scan

$$\text{Midline shift at } P_1 \text{ in B-scan} = \frac{c_{sin} - c_{dx} + oe}{2}$$

$$\text{and at } P_2 = \frac{a_{sin} - a_{dx} + oe}{2}$$

oe = oedema of the scalp in A-scan, taken as a positive value when on the right and as a negative value when on the left *(Fig 7)*

The septum pellucidum The thickness of the septum pellucidum was calculated as the difference between the head diameter measured by the transmission method and the sum of the distances between the initial echo and the midline echo measured from both sides at test point P_2.

$$\text{Septum pellucidum} = d - (a_{dx} - a_{sin}) \quad \textit{(Fig 7)}$$

The temporal horn The thickness of the brain mantle was determined as the distance between the external echo of the contralateral temporal horn and the end echo on each side in both A-scan and B-scan recordings

$$\text{Brain mantle} = g - f \qquad \textit{(Fig 7)}$$

The brain mantle index (BMI) was calculated as the relation between the distance from the midline echo to the end echo and the thickness of the brain mantle determined as mentioned above (177)

$$\text{BMI} = \frac{g - c}{g - f} \qquad \textit{(Fig 7)}$$

The index for the thickness of the brain mantle was also calculated as the reciprocal of the BMI (58)

$$\text{Reciprocal BMI} = \frac{g - f}{g - c} \qquad \textit{(Fig 7)}$$

To exclude the influence of the inaccuracy of the end echo on the BMI in B-scan examinations another index suggested earlier by Valkeakari (200) was also calculated as the relation between the distance from the initial echo to the external echo of the contralateral temporal horn and the bitemporal diameter of the head at test point P_1 The contralateral temporal horn index (CTHI)

$$= \frac{f}{c_{dx} + c_{sin}} \qquad \textit{(Fig 7)}$$

The body of the lateral ventricle The width of the body of the contralateral lateral ventricle was determined on right-to-left and left-to-right tracings in both A-scan and B-scan. The common width of the bodies was calculated and the results in A-scan and B-scan were compared with one another and with the results at the different testing moments.

The common width of the bodies =

$$(b_{dx} - a_{dx}) + (b_{sin} - a_{sin}) = (b_{dx} + b_{sin}) - (a_{dx} + a_{sin}) \qquad \textit{(Fig 7)}$$

The lateral ventricle index (LVI) (181) was calculated as the relation between the common width mentioned above and the diameter of the head at test point P_2 in both A-scan and B-scan.

$$\text{LVI} = \frac{(b_{dx} + b_{sin}) - (a_{dx} + a_{sin})}{a_{dx} + a_{sin}} \quad \textit{(Fig 7)}$$

To avoid the possibile error in determining the head diameter LVI was calculated in A-scan using also the head diameter (d) obtained by the transmission method instead of ($a_{dx} + a_{sin}$)

$$LVI = \frac{b_{dx} + b_{sin} - d}{d} \qquad (Fig\ 7)$$

It is to be noted that d includes the thickness of septum pellucidum, which the sum $a_d + a_{sin}$ does not include. On the other hand, the sum $b_{dx} + b_{sin}$ includes twice the thickness of septum pellucidum.

The results obtained in A-scan and B-scan were compared with one another and with the results obtained at the various testing moments during the study

E. IDENTIFICATION OF THE VENTRICULAR ECHOES

In the present study the source of the echoes taken to be the lateral ventricle echo and the temporal horn echo was identified by injecting

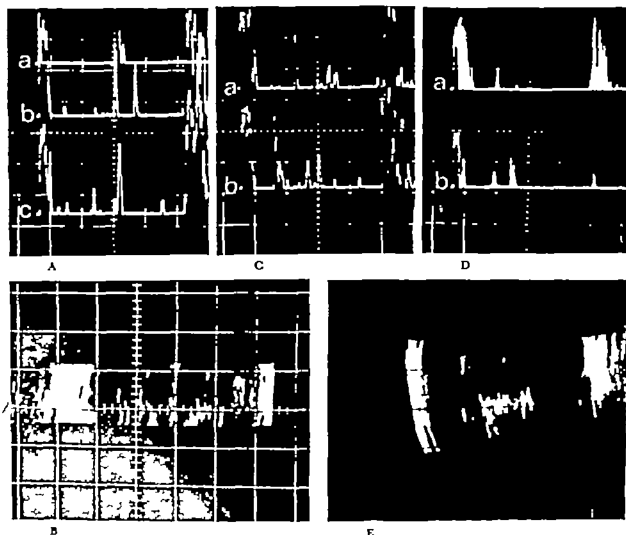


Fig 10 Pos[illegible] stem exa[illegible] of [illegible] newborn infant, who died [illegible] the age of tw[illegible] days.
A. A-scan, [illegible] midline [illegible] control by [illegible] the transmission method, b) the body echoes of the lateral [illegible] entricles, [illegible]) the temporal horn echoes B B-sc[illegible] coronal plane C. A-scan, after 10 ml of C. S. F had been replaced by 10 ml of air [illegible] the bod[illegible] [illegible] entricles, the [illegible]pulateral body gives now [illegible] strong echo, b) the temporal horn echoes, the [illegible] [illegible] strong echo D A-sca[illegible] on th[illegible] storage tube, 20 ml of air injected, [illegible]) the body echo of [illegible] [illegible] b [illegible] the [illegible]pula[illegible]eral temporal horn echo and the echo of circumpeduncular cistern.
E. B-scan, coronal [illegible]

air into the cerebral ventricles of a newborn infant who died at two days without having any neurological disease. The examination was performed 4.5 to 6 hours after death The right-to-left tracings were first made from test points P_1 and P_2 in A-scan Then also the right coronal scan was made in B-scan *(Fig 10 A B)* The echograms obtained from this dead infant did not differ from those recorded in the living subjects, which agrees with the observations made by Lithander (139) After 10 ml of C S F had been replaced by 10 ml of air injected into the ventricles by means of a neck puncture a much stronger echo than usual was seen in the place of the temporal horn echo and of the echo of the body of the lateral ventricle, on the ipsilateral side *(Fig 10 C)* After injecting further more 10 ml of air into the ventricular system a strong echo was obtained from the place of the ipsilateral temporal horn echo in addition, a constant echo was noted 1,2 cm deeper obviously originating in the ipsilateral circumpeduncular cistern (6) After the second injection of air the echo from the body of the ipsilateral lateral ventricle was shifted 3 mm laterally into a place where no echo was observed before *(Fig 10 D E)* This observation agrees with the results of Krüger (127) concerning the hypothesis of the possibility to blow the cerebral ventricles up during pneumoencephalography

F THE DETERMINATION ERROR

To measure the determination error one subject of the study aged six days was examined 12 times successively in A-scan and in B-scan within one hour The probe was laid aside and the infant was taken away from the examination table between each new examination. On the basis of these examinations standard deviations were calculated for the distances measured in the pictures and also for the values calculated on the basis of the measurements both in A-scan and in B-scan

G STATISTICAL METHODS

The calculations were performed with an electronic calculator Compucorp 140 Statistician, giving automatically the mean ($\bar{x}$) the standard deviation (SD) the correlation coefficient (r) and the linear regression equation

In the standard deviations (SD) given with the results the determination error is taken into consideration.

The significance of the differences of the means was tested by the Student's t test. Different formulas were used depending on whether the samples were independent or not.

The samples are not independent when the results of measurements performed on one subject using two different methods are compared Neither are they independent when comparison is made between the results of the same population obtained at various ages using the same method of examination.

The ChiSquare test was used to test the differences of the distribution of the lateral ventricle indices between A-scan and B-scan.

The significance of the differences was stated as follows

If the risk (p) was

$p \leq 0.001$	the difference was called highly significant
$0.001 < p \leq 0.01$	the difference was called significant,
$0.01 < p \leq 0.05$	the difference was called almost significant,
$p > 0.05$	the difference was not significant.

If not otherwise mentioned, the means and the standard deviations of the means are the values given in the presentation of the results.

Table 3 a. The determination error in mm for the measured distances.

Distance	A-scan	B-scan
a	0.4	0.6
b	0.5	0.6
c	0.5	0.8
d	0.5	—
	0.4	0.4
f	0.5	0.6
g	0.9	0.8

Table 3 b. The determination error for the values calculated on the basis of the measured distances. The distances are expressed as mm.

	A-scan	B-scan
Shift of the midline at P	0.5	0.8
Shift of the midline at P	0.6	0.5
Diameter of the head at P	0.8	0.7
Diameter of the head at P	0.5	0.6
Diameter of the bodies of the lateral ventricles	0.7	1.1
Diameter of single body	0.4	0.7
Lateral ventricle index	0.008	0.015
Thickness of the brain mantle	1.1	0.9
Brain mantle index	0.12	0.12
Contralateral temporal horn index	0.009	0.006
Head wall thickness at P	0.[illegible]	0.8
Head wall thickness at P	0.7	0.9
Thickness of septum pellucidum	0.8	1.0
Oedema of the scalp at P	0.6	—
Oedema of the scalp P	0.4	—

A. THE DETERMINATION ERROR

The determination errors for the measured distances are shown in *Table 3a* and the errors for the values calculated on the basis of the measurements in *Table 3b*. The determination errors in A-scan and in B-scan did not differ statistically from one another in any of the paired values. The determination error has been regarded in the standard deviation values presented later.

B. THE DIAMETER OF THE HEAD

Test point P_1. Measurements of the diameter of the head at test point P_1 gave the results shown in *Tables 4a and 4b*. If the scalp oedema was not excluded a decrease of 1.3 mm in A-scan and 1.6 mm in B-scan in the head diameter was registered between the ages of three hours and two days. In both A- and B-scans the difference between the first measurement at the age of three hours and that at the age of 24 hours was statistically significant ($p < 0.01$). At the age of two days the difference was highly significant ($p < 0.001$).

When the scalp oedema was excluded, the head diameter in A-scan showed a similar decrease as the measurements including the scalp oedema. The highest value was registered at the age of six hours and the lowest at the age of two days. The difference between the highest and lowest value was highly significant ($p < 0.001$). The difference between the head diameters at the ages of three hours and two days was significant ($p < 0.01$). A significant decrease ($p < 0.01$) was also noticed between th

Table 4 a. Head diameter in mm ± SD at various ages during the first week of life at test point P

Age	Scalp oedema included		Scalp oedema excluded
	A-scan	B-scan	A-scan
3 hrs	93.3 ± 4.2	94.0 ± 3.7	92.1 ± 4.2
6 hrs	93.3 ± 3.9	93.5 ± 3.8	92.3 ± 3.9
12 hrs	92.9 ± 4.2	93.4 ± 3.9	91.8 ± 4.3
24 hrs	92.2 ± 4.0	92.9 ± 3.6	91.1 ± 3.9
2 days	92.0 ± 4.2	92.4 ± 3.7	90.9 ± 4.2
4 days	92.4 ± 4.1	92.4 ± 4.0	91.1 ± 4.1
6 days	92.4 ± 3.7	92.7 ± 3.6	91.0 ± 3.4

Table 4 b. Changes of head diameter in mm ± SD at test point P

Age	Scalp oedema included		Scalp oedema excluded
	A-scan	B-scan	A-scan
3 hrs → 2 days	− 1.3 ± 2.5 $p < 0.001$	− 1.6 ± 2.1 $p < 0.001$	− 1.2 ± 2.8 $p < 0.01$
2 days → 6 days	+ 0.4 ± 1.9 $p > 0.05$	+ 0.3 ± 1.5 $p > 0.05$	+ 0.1 ± 2.5 $p > 0.05$

maximum value at the age of six hours and the value at the age of 24 hours

The slight increase in the diameter of the head at test point P_1 after the age of two days was not significant by any if the methods mentioned above.

The changes in the diameter of the head at test point P_1 are seen in *Fig. 11*

Test point P_2. Measurements of the diameter of the head at test point P_2 gave the results shown in *Tables 5a and 5b* A decrease of 1.4 mm between th ages of three hours and two days was noticed in the head diameter in A-scan. The decrease was highly significant ($p < 0.001$) as was also the difference between the values at the ages of three hours and 24 hours. There was a highly significant ($p < 0.001$) increase of 1.1 mm in the head diameter at test point P_2 in A-scan between the ages of two days and six days.

In B-scan a highly significant ($p < 0.001$) decrease of 1.2 mm n the head diameter was noticed at test point P_2 between th ages of three hours and two days. There was already a significant difference ($p < 0.01$) in the head diameter between the ages of three hours and 24 hours. After the age of two days an increase,

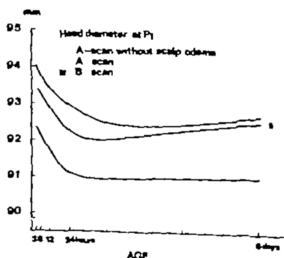


Fig. 11 Changes of the head diameters during the first week of life as determined t est point P by different methods.

Table 5 a. Head diameter in mm ± SD at various ages during the first week of life at test point P

Age	Scalp oedema included		Scalp oedema excluded
	A-scan	B-scan	A-scan
3 hrs	92.7 ± 3.6	9_2 ± 3.4	91.8 ± 3.5
6 hrs	92.3 ± 3.7	91 7 ± 3.1	91 1 ± 3.9
12 hrs	92.1 ± 3.6	91 6 ± 3.5	90.8 ± 3.7
24 hrs	91 6 ± 3.7	91 4 ± 3.9	90.6 ± 3.8
days	91.3 ± 3.9	91 0 ± 3.4	90.4 ± 4.1
4 days	91 4 ± 3.6	91.2 ± 3.6	90.4 ± 3.7
6 days	92.4 ± 3.7	91 6 ± 3.5	91 4 ± 3 7

Table 5 b. Changes of head diameter in mm ± SD t test point P

Age	Scalp oedema included		Scalp oedema excluded
	A-scan	B-scan	A-scan
3 hrs → days	− 1 4 ± 2.0 $p < 0.001$	− 1_ ± 1.8 $p < 0.001$	− 1 4 ± 2.3 $p < 0.001$
2 days → 6 days	− 1 1 ± 1 6 $p < 0.001$	− 0.6 ± 1 7 $p < 0.02$	− 1.0 ± 1.9 $p < 0.001$

significant at $p < 0.02$ level, was noticed during the next four days by the age of six days in B-scan. In A-scan, with the scalp oedema excluded a decrease of 1 4 mm, similar to the one described above in A-scan, was noticed between the ages of three hours and two days. An increase of 1 1 mm was observed in the head diameter between the ages of two days and six days. Both changes were highl significant ($p < 0.001$) The changes in the head diameter measured at test point P_2 by the arious methods described above are seen in *F* *1*

The transmission thod indi ated n the head diameter measured at test point P_2 a decrease of 1 4 mm between the ag s of t ree hours and two da s Th decrease was h gh1 sign ficant $p < 0.001$ w as th diff n between the ages f three ho nd 24 n u s A h ghl significant p (n in e 1 J mm was noticed in th head d amete betwee th ages of two da s da b t tr nsmission method The hang u th d diam ter b

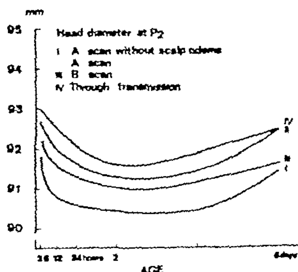


Fig 12 Changes of the head diameters during the first week of life as determined at test point P by different methods.

the transmission method are seen in *Tables 6a and 6b* and *F g 12*

No difference between the alues of the head

Table 6 a. Head diameter in mm ± SD t various ges during the first week of life at test point P by the transmission method

Age	Head diameter
3 hrs	93.0 ± 3.7
6 hrs	92.9 ± 3.5
12 hrs	92.5 ± 3.7
24 hrs	92.1 ± 3.5
2 days	91.6 ± 3.5
4 days	92.1 ± 3.4
6 days	92.4 ± 3.5

Table 6 b. Changes of head diameter in mm ± SD t test point P by the transmission method

Age	Difference
3 hrs → 2 days	−1 4 ± 1.6 $p < 0.001$
2 days → 6 days	+ 0.7 ± 1.3 $p < 0.001$

diameter in the infants of primipara and those of multiparae was observed by the various methods during the first week of life.

There was an average difference of 0.4 ± 0.3 mm between the head diameter in B-scan and that in A-scan at test point P_1 and on of −0 4 ± 0.2 mm at test point P_2. The difference between the head diameter in the transmission method and that in A-scan was on the average 0.4 ± 0.2 mm As fa as the results obtained by the various methods are concerned, the differences are not significant. The head diameter was on the average 0 7 ± 0.3 mm larger at test point P_1 than at test point P_2 in A-scan. In B-scan the difference was 1.3 ± 0.3 mm, respectively

The gression equations The linear regression equations between birth weight, height t birth and head circumference on one hand and on th other hand the head diameter was calculated by using the value of head diameter obtained at the age of three hours t test point P with the scalp oedema excluded. Th values are given below with the respective standard errors.

The linea regression equation between birth weight and the head diameter gave the formula y = (683 ± 20) x − 2 780. The Pearsonian product moment correlation coefficient (r) was 0 437 ± 0 128 The regression equation is shown in *Fig 13.* The linear regression equation calculated between height at birth and the head diameter is presented by the formula y = (2.58 ± 0 07) x + 26.91 The correlation coefficient (r) was 0 459 ± 0 130 The regression equation is shown in *Fig 14* The linear regression equation between head circumference and the head *diameter* gave the formula y = (2.23 ± 0 05) x + 14 09 and the correlation coefficient (r) the value of 0.516 ± 0 125 The regression equation is shown in *Fig 15.*

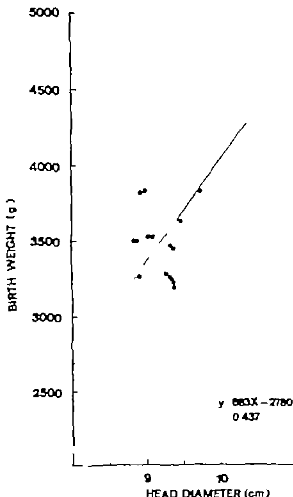


Fig 13. Correlation between birth weight and the head diameter (scalp oedema excluded) the ge of 3 hours in A-scan at test point P_2.

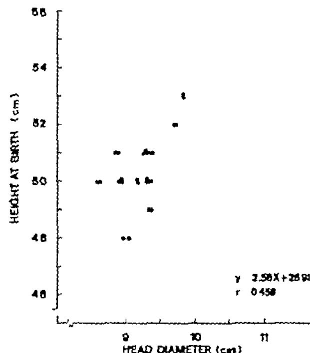


Fig. 14. Correlation between height at birth and the head diameter

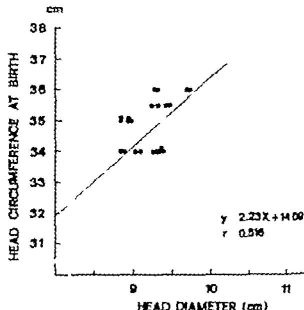


Fig. 15. Correlation between the head circumference at birth and the head diameter

C. OEDEMA OF THE SCALP

The caput succedaneum did not lie in the area of the test points. Slight oedema of the scalp was, however, observed also at the test points. The average thickness of the scalp oedema did not vary during the first week of life *(Tables 7a and 7b)*. There were no statistical differences between the thickness of the scalp oedema on either side or between test points P_1 and P_2. No significant correlation between the side of the oedema of the scalp and the foetal position in utero was observed.

Table 7 a. Thickness of the scalp oedema in mm ± SD at test point P

Age	N oedema	Oedema on the right side		Oedema on the left side		Total	
	N	N		N		N	
3 hrs	5	24	1.1 ± 0.9	22	1.5 ± 1.0	51	1.2 ± 1.2
24 hrs	2	23	1.1 ± 0.9	26	1.3 ± 1.0	51	1.1 ± 1.2
6 days	1	21	1.2 ± 0.8	29	1.5 ± 0.9	51	1.3 ± 1.1

Table 7 b. Thickness of the scalp oedema in mm ± SD at test point P

Age	N oedema	Oedema on the right side		Oedema on the left side		Total	
	N	N		N		N	
3 hrs	7	17	1.1 ± 1.1	27	1.1 ± 0.8	51	0.9 ± 1.0
24 hrs	4	25	1.0 ± 0.6	22	1.0 ± 0.5	51	0.9 ± 0.8
6 days		19	1.2 ± 0.8	30	0.9 ± 0.8	51	1.0 ± 0.9

Table 8 a. Head wall thickness ± SD in mm. Mean values of 1 7 examinations at test point P and P_2. Scalp oedema excluded

	A-scan	B-scan
Test point P	4.6 ± 2.0	5 6 ± 1 7
Test point P	4.2 ± 1.8	4 1 ± 1.8

Table 8 b. Significance between head wall thickness I A-scan and B-scan t test point P and P

	A-scan at P	B-scan t P
A-scan at P	$p > 0.05$	$p > 0.05$
B-scan t P	$p < 0.01$	$p < 0.001$

Table 8 c. The superficial structure index of Sjogren

	A-scan	B-scan
Test point P	0.050 ± 0.019	0.060 ± 0.016
Test point P	0.046 ± 0.017	0.046 ± 0.016

D THE HEAD WALL

Measurements of the head wall thickness, excluding the scalp oedema, revealed at test point P_1 a mean value of 4 6 ± 2.0 mm in A-scan and 5 6 ± 1 7 mm in B-scan. At test point P_2 the head wall thickness was 4.2 ± 1.8 mm in A-scan and 4 1 ± 1.8 mm in B-scan The bove values are the mean values of the seven registrations during the first week of life *(Table 8a)*

There was a significant difference ($p < 0.01$) between th values in A-scan and B-scan at test point P_1 At test point P_2 the difference in head wall thickness between A-scan and B-scan was not significant. There was no statistical difference in the head wall thickness between P_1 and P_2 in A-scan. In B-scan a highly significant difference ($p < 0.001$) between th head wall thickness at test points P and P was noticed *(Table 8b)* Th superficial structure index (181) calculated on the basis of the head wall thickness is seen in *Table 8c*

E. THE POSITION OF THE MIDLINE

The amount of th average midline shift did not exceed 1 1 mm to either side. The mean of the values of the midline shift, when the shift to the right was indicated as a positive value and th shift to the left as a negative value, did not differ more than 0.3 mm from the theoretical midline in the whole series in A-scan as well as in B-scan. There was no statistical difference in the amounts of the midline shift during the first week of life in the whole group The results of A-scan and B-scan examinations did not differ significantly from one another Nor was there any statistical differences between the shifts registered at test points P_1 and P_2 *(Tables 9a and 9b)*

Th actual difference between the mounts of the midline shift in A-scan and n B-scan (gi en as an absolute value) was on the average 0 6 ± 0.4 mm at test point P nd 0 6 ± 0.5 mm at test point P_2.

The midline shifts registered at P_2 and classified on th basis of the foetal position in utero in

Table 9 a. Shift of the midline in mm ± SD at test point [illegible]

Age	Method	No shift	Shift to the right side		Shift to the left side		Mean + shift to the right − shift to the left	Range + shift to the right − shift to the left
		N	N		N			
3 hrs	A-scan	5	23	1.0 ± 0.8	23	0.6 ± 0.6	+ 0.2 ± 1.0	− 1.6 — + 3.0
	B-scan	1	8	0.9 ± 0.8	22	0.7 ± 0.5	+ 0.2 ± 1.1	− 1.5 — + 2.5
6 hrs	A-scan	3	29	0.9 ± 0.8	19	0.7 ± 0.6	+ 0.3 ± 1.0	− 1.8 — + [illegible]
	B-scan	0	34	0.8 ± 0.8	17	0.6 ± 0.6	+ 0.3 ± 1.1	− 1.8 — + 2.2
12 hrs	A-scan	4	26	0.8 ± 0.6	21	0.9 ± 0.8	+ 0.0 ± 1.1	− 2.5 — + 1.7
	B-scan	5	24	0.9 ± 0.8	22	1.1 ± 0.9	− 0.1 ± 1.3	− 3.0 — + 2.6
24 hrs	A-scan	2	22	0.8 ± 0.7	27	0.7 ± 0.6	− 0.0 ± 1.1	− 1.5 — + 2.0
	B-scan	3	25	0.8 ± 0.7	23	0.9 ± 0.6	+ 0.0 ± 1.0	− 2.4 — + 2.1
2 days	A-scan	4	22	0.9 ± 0.7	25	0.8 ± 0.7	− 0.0 ± 1.1	− 2.9 — + 1.9
	B-scan	4	18	0.8 ± 0.8	29	0.8 ± 0.8	− 0.2 ± 1.1	− 2.3 — + 2.1
4 days	A-scan		30	0.7 ± 0.6	19	0.7 ± 0.6	+ 0.2 ± 0.9	− 1.4 — + 2.8
	B-scan	2	[illegible]	0.9 ± 0.8	24	0.9 ± 0.8	+ 0.0 ± 1.[illegible]	− 1.9 — + 2.3
6 days	A-scan	2	25	0.6 ± 0.6	24	1.0 ± 0.7	− 0.1 ± 1.1	− 2.6 — + 1.6
	B-scan	0	19	0.8 ± 0.7	32	0.9 ± 0.7	− 0.2 ± 1.0	− 2.2 — + 2.1

Table 9 b. Shift of the midline in mm ± SD at test point P

Age	Method	No shift	Shift to the right side		Shift to the left side		Mean + shift to the right − shift to the left	Range + shift to the right − shift to the left
		N	N		N			
3 hrs	A-scan	4	21	1.0 ± 0.7	6	0.7 ± 0.6	+ 0.1 ± 1.1	− 1.7 — + 2.0
	B-scan	3	22	0.8 ± 0.7	26	0.8 ± 0.7	− 0.1 ± 1.1	− [illegible]7 — + 2.2
6 hrs	A-scan	5	23	0.9 ± 0.9	23	0.7 ± 0.6	+ 0.[illegible] ± 1.1	− 1.4 — + 3.5
	B-scan	1	25	0.6 ± 0.4	25	0.7 ± 0.6	+ 0.1 ± 1.2	− 1.8 — + 3.9
12 hrs	A-scan	6	4	1.0 ± 0.8	21	0.9 ± 0.8	+ 0.1 ± 1.2	− 2.8 — + 2.9
	B-scan	0	23	0.8 ± 0.5	28	1.0 ± 0.9	− 0.1 ± 1.2	− 2.9 — + 1.5
24 hrs	A-scan	4	24	0.7 ± 0.7	23	0.8 ± 0.7	− 0.1 ± 1.0	− 1.9 — + 1.7
	B-scan		26	0.6 ± 0.6	23	0.8 ± 0.7	− 0.1 ± 1.0	− 2.4 — + 2.1
2 days	A-scan	3	[illegible]	0.6 ± 0.6	23	0.6 ± 0.6	+ 0.0 ± 0.8	− 1.3 — + 1.3
	B-scan	2	23	0.6 ± 0.5	26	0.6 ± 0.5	− 0.0 ± 0.8	− 1.6 — + 2.1
4 days	A-scan	7	20	0.7 ± 0.6	24	0.7 ± 0.6	− 0.0 ± 0.9	− 1.7 — + 2.1
	B-scan	2	19	0.6 ± 0.5	30	0.7 ± 0.7	− 0.[illegible] ± 0.9	− 2.5 — + 1.2
6 days	A-scan	1	30	0.7 ± 0.6	20	0.9 ± 0.9	+ 0.0 ± 1.1	− 3.0 — + 1.7
	B-scan	5	19	0.6 ± 0.5	27	0.7 ± 0.7	− 0.2 ± 0.9	− 2.6 — + 1.4

infants having had cephalic presentation and vaginal delivery are shown in *Table 10*. In those infants born in the I position (occiput to the left) a slight midline shift to the right was generally noticed during the first day of life both in A-scan and in B-scan. In infants born in the II position (occiput to the right) a corresponding slight midline shift to the left was observed. The shifts were largest at the ages of six hours and 12 hours. The difference in the amounts of the shifts between the infants born in the I position and those born in the II position was calculated to be almost significant ($p < 0.05$) both in A-scan and in B-scan at the ages

Table 10 Influence of the foetal position in utero on the midline shift at test point P (vaginal delivery cephalic presentation)

+ = Shift to the right, — = Shift to the left.

Age	Method	Foetal position				Significance
		Left N = 26		Right N = 17		
		Mean ± SD	Range	Mean ± SD	Range	
3 hrs	A-scan	+ 0.2 ± 0.9	− 1.0 — + 2.0	− 0.1 ± 1.2	− 1.7 — + 1.7	
	B-scan	+ 0.2 ± 0.9	− 1.4 — − 2.0	− 0.1 ± 1.3	− 2.7 — + 2.2	
6 hrs	A-scan	+ 0.4 ± 1.3	− 1.2 — + 3.5	− 0.2 ± 0.8	− 1.4 — + 0.8	$p < 0.05$
	B-scan	+ 0.4 ± 1.3	− 1.3 — + 3.9	− 0.3 ± 0.8	− 1.8 — + 1.6	$p < 0.05$
12 hrs	A-scan	+ 0.4 ± 1.1	− 2.0 — + 2.9	− 0.4 ± 1.1	− 2.8 — + 1.8	$p < 0.05$
	B-scan	+ 0.2 ± 1.3	− 2.9 — + 1.5	− 0.5 ± 1.1	− 2.6 — + 1.3	$p < 0.05$
24 hrs	A-scan	+ 0.1 ± 1.1	− 1.9 — + 1.7	− 0.0 ± 1.0	− 1.7 — + 1.7	
	B-scan	− 0.0 ± 1.1	− 2.1 — + 2.1	− 0.0 ± 1.1	− 2.4 — + 1.5	
2 days	A-scan	+ 0.2 ± 0.7	− 1.5 — + 1.3	− 0.2 ± 0.8	− 1.3 — + 1.2	
	B-scan	+ 0.2 ± 0.8	− 1.0 — + 2.1	− 0.2 ± 0.7	− 1.6 — + 0.3	
4 days	A-scan	− 0.1 ± 1.0	− 1.7 — + [illegible]	− 0.0 ± 0.9	− 1.5 — + 1.3	
	B-scan	− 0.1 ± 0.9	− 2.5 — + 1.0	− 0.1 ± 0.9	− 1.9 — + 1.2	
6 days	A-scan	+ 0.2 ± 0.9	− 1.8 — − 1.4	− 0.0 ± 1.3	− 3.0 — + 1.7	
	B-scan	− 0.0 ± 0.8	− 1.5 — − 1.2	− 0.3 ± 1.1	− 2.6 — + 1.4	

of six hours and 12 hours. The direction of the midline shift was in both groups to that side of the head lying close to the maternal abdominal wall. After the first day of life no statistical differences were observed. Results obtained at test point P_1 did not show any changes concerning the midline shift similar to those observed at test point P_2.

There was a considerable number of newborn infants who expressed a midline shift greater than 2 mm at one or both of the test points sometimes during the first week of life. At the age of 12 hours as many as six newborns in A-scan and seven in B-scan of all 51 infants showed a midline shift which exceeded 2 mm. The number of cases with midline shift of more than 2 mm t different ages is presented in *Table 11*. The range of the midline shifts in A-scan and in B-scan at test points P and P_2 is given in *Tables 9a and 9b*.

When th limits for the normal distribution of the midline shift were calculated by the formula 2.58 SD which secures 99 per cent of the newborns within these limits, an average value of 3 mm was obtained for both test points and methods.

Table 11 The total number of newborns in the series of 51 infants with midline shift of more than 2 mm during the first week of life at test points P and P_2.

Age	A-scan	B-scan
3 hrs	3	4
6 hrs	4	3
12 hrs	6	7
24 hrs	1	3
2 days	1	3
4 days	2	2
6 days	3	3

F THE SEPTUM PELLUCIDUM

The mean valu for the thickness of the septum pellucidum in all successive examinations was 0.4 ± 1.2 mm in A-scan and 0.9 ± 1.2 in B-scan. The values did not change significantly during the first week of life. Altogether 4 newborns n A-scan and 7 newborns in B-scan had a septum pellucidum more than 2mm thick. The highest alue was 6.3 mm *(Fig 16)*

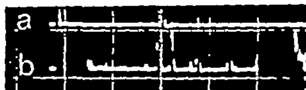




Fig 16. A case of cyst of septum pellucidum. Upper screen: a) the midline control, b) echoes from the cyst in the middle of the right-to-left tracing. Lower screen: Righ coronal B-scan showing a pair of echoes above the midlin echo.

G THE TEMPORAL HORN

The brain mantle The thickness of the brain mantle, measured as the distance between the contralateral temporal horn echo and the end echo is given in *Table 12* The mean thickness of the brain mantle in all examinations was 18.2 ± 2 1 mm in A-scan and 16.9 ± 2.0 mm in B-scan. The difference between A-scan and B-scan was significant at $p < 0\ 01$ level. However no statistically significant differences were found between the right and left side or between the successive examinations in the same patient.

The brain mantle index (BMI) The calculations of the brain mantle index (BMI) (177) gave the mean value of 2 28 ± 0.20 in A-scan and 2.39 ± 0.21 in B-scan for the first week of life. The difference between A-scan and B-scan was significant at $p < 0\ 01$ level. The BMI values at the various ages during the first week are given in *Table 13a* No statistical difference was observed between the BMI values of the successive examinations either in A-scan or in B-scan.

The reciprocal brain mantle index. An index calculated as the reciprocal of the BMI (38) expressed values shown in *Table 13b* The mean value for the first week of life was 0 44 ± 0 03 in A-scan and 0 42 ± 0.03 in B-scan. The difference between A-scan and B-scan was significant at $p < 0\ 01$ level. There were no statistical differences either in A-scan or in B-scan between the successive examinations during the first week of life.

The contralateral temporal horn index (CTHI) As suggested earlier by the author (200) a new method was used for calculating an index to indicate the position of the temporal horn. The mean index value of 0 748 ± 0 017 was obtained in A-scan and 0 751 ± 0 015 in B-scan for

Table 12. The thickness of the brain mantle. The mean of the left and right side values in mm ± SD

Age	3 hrs	6 hrs	12 hrs	24 hrs	2 days	4 days	6 days	Mean
A-scan	18.4	18.1	18.0	18.1	18.4	18.0	18.2	18.2
± SD	1.9	2.3	2.0	1.9	2.2	2.3	1.9	2.1
B-scan	17 0	17 1	16.7	16.8	16.7	17 1	17 1	16.9
± SD	1.9	2.2	1 9	2.0	2.1	2 1	2.0	2.0

Table 13 The brain mantle index (BMI)

Age	3 hrs	6 hrs	12 hrs	24 hrs	2 days	4 days	6 days	Mean
A-scan	2.28	2.30	2.30	2.28	2.25	2.29	2.27	2.28
± SD	0 19	0.22	0 19	0.19	0 21	0.23	0.20	0.20
B-scan	2.41	2.39	2.40	2.40	2 41	2.37	2.36	2.39
± SD	0.19	0.23	0.20	0 20	0.22	0.20	0.19	0.21

Table 13 b The reciprocal brain mantle index

Age	3 hrs	6 hrs	12 hrs	24 hrs	2 days	4 days	6 days	Mean
A-scan	0.44	0.44	0.44	0.44	0.45	0 44	0.44	0.44
± SD	0.03	0.04	0.03	0.03	0 04	0 04	0.03	0.03
B-scan	0.42	0.42	0.42	0.42	0.42	0.42	0.43	0.42
± SD	0.03	0.04	0.03	0.03	0.03	0.03	0.03	0.03

Table 13 c. The contralateral temporal horn index (CTHI)

Age	3 hrs	6 hrs	12 hrs	24 hrs	2 days	4 days	6 days	Mean
A-scan	0.749	0.749	0.749	0.750	0.746	0.748	0.748	0.748
± SD	0.016	0.017	0.017	0.017	0 017	0.017	0.018	0.017
B-scan	0 752	0 752	0.748	0 751	0.750	0.751	0.749	0.751
± SD	0.015	0.015	0.013	0.014	0.016	0.015	0.014	0.015

all examinations during the week of investigat ion. The difference between A-scan and B-scan values was not statistically significant. The values remained statistically stable during the whole week in A-scan and in B-scan as shown in *Table 13c*

Common features for all indices of the temporal horn Independently of the method used for calculat ions of the indices, differences between the index values of the left side and the right side were not found. Neither was there any difference as a consequence of the foetal position in utero during the delivery Between the newborns of primiparae and multiparae no difference was observed in any of th indices calculated on th basis of the temporal horn echo.

The standard deviation of the indices calculat ed on the basis of the temporal horn echo was proportionally lowest for the contralateral temporal horn index. The difference was highly significant ($p < 0\,001$) when compared with the standard deviations of the BMI and the reciprocal BMI values.

H. THE BODY OF THE LATERAL VENTRICLE

The diameter f the bodies. The mean of the common diameter of the lateral ventricles was 28.7 ± 2.3 mm in A-scan and 29 0 ± 2 1 mm in B-scan during the first week of life. When calculating the same diameter with the aid of tl head diameter as measured by the transmissi method, the mean value of 28.2 ± 2 3 mm f the whole week was obtained The values of th common diameter of the bodies are shown i *Table 14* The values obtained by the variou methods did not differ statistically from on another Neither was there any statistical differ

Table 14 The common diameter of the bodies of the lateral ventricles in mm ± SD

Age	3 hrs	6 hrs	12 hrs	24 hrs	2 days	4 days	6 days	Mean
A-scan	29.1	29 0	29.3	29.3	28.5	28.5	27.5	28.7
± SD	2.6	2.0	2.3	2.4	2.3	2.0	2.3	2.3
A/Thru	28.6	28 3	28.9	28.2	28.2	27.9	27.6	28 2
± SD	2.6	2.1	2.2	2.5	2.2	2.1	2.1	2.3
B-scan	29.5	29 1	28.5	28.7	29 0	29 0	28.9	29.0
± SD	2.3	2.3	2.0	2.0	2.1	1.9	2.0	2.1

ence between the successive values obtained by each method during the first week of life. No statistical difference was observed between the values of the infants of primiparae and multiparae. Nor was there any statistical difference between the values of boys and girls.

The mean diameter of a single body was 14.4 ± 1.5 mm in A-scan and 14.4 ± 1.3 mm in B-scan. When comparing the diameter of the body of the left and the right lateral ventricle, no significant difference was observed during the study. The foetal position in utero during the delivery did not produce any statistical difference in the ventricular size.

The lateral ventricle index. The index values at the different ages during the study calculated by three different ways are given in *Table 15*. If the sum of the distances from the initial echo to the midline echo on each side was used as the divisor, the LVI got the mean value of 0.313 ± 0.027 for the whole first week of life. Similarly, if the diameter of the head obtained by the transmission method was used as divisor, the corresponding value was 0.306 ± 0.026. The difference was not significant. The mean value obtained by B-scan (0.316 ± 0.023) did not differ statistically from the corresponding A-scan value. The indices of the successive examinations during the first week of life did not differ statistically from the respective mean values, irrespective of the method used. The cumulative distribution of the LVI values in A-scan and in B-scan for the whole first week of life is seen in *Fig. 17*. The distribution of the index values between A-scan and B-scan did not show any statistical difference (the Chi Square test (χ^2 = 7.58, f = 4, p > 0.1). The differences between the values of infants of primiparae and multiparae were not significant. The lateral ventricle index between boys and girls did not show any statistical difference.

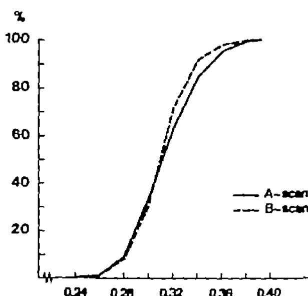


Fig. 17. Cumulative distribution of the lateral ventricle index values of the whole study in A-scan and B-scan (χ^2 = 7.58, f = 4, p > 0.1)

I. ABNORMAL FINDINGS

No cases of hydrocephaly, hydranencephaly or porencephaly were found. A diagnosis of subdural bleeding was neither made during the study. One symptomless case with a constant double echo in the place of the septum pellucidum echo was found. The finding was interpreted as a cyst of the septum pellucidum *(Fig. 16)*.

Table 15. The lateral ventricle index (LVI)

Age	3 hrs	6 hrs	12 hrs	24 hrs	2 days	4 days	6 days	Mean
A-scan	0.314	0.315	0.320	0.321	0.314	0.312	0.298	0.313
± SD	0.028	0.025	0.030	0.029	0.030	0.023	0.027	0.027
A/Thru	0.307	0.305	0.310	0.306	0.308	0.303	0.290	0.306
± SD	0.029	0.024	0.028	0.028	0.025	0.021	0.029	0.026
B-scan	0.320	0.317	0.312	0.313	0.318	0.317	0.315	0.316
± SD	0.024	0.025	0.025	0.023	0.023	0.019	0.025	0.023

VII DISCUSSION

DISCUSSIO\ OF THE SUBJECTS OF THE PRESE\T STUD\

be means and standard deviations of the h weights, heights at birth and head circumnces at birth *(Table 2)* agree with values ,iously obtained from Finnish infants (32, 170 194) During the period of the study gether 325 infants were born in 318 deliver The distribution of the methods of delivery not differ notabl) between the study group all the other infants born over the study od in the same hospital. The greater than nal number of breech presentations and s will be explained by the nature of the ital as a University Central Hospital collect the more complicated cases from th minor itals. The Apgar score among the altogether infants was on th average 8.64 ± 1.2. m those eight infants, whose Apgar score less than 6 and also the subjects belonging e study were excluded, the Apgar score for he others was 8.79 ± 0.79 Thus, concern the Apgar score, determined at the age of ec, the subjects of the study did not differ the average.

I. DISCUSSIO\ OF THE METHODS

he diameter f the head. Methods using other ns than ultrasound *e g* calliper measure ts, for determining the diameter of the head excluded from th present study Also hod adding a constant to the distance veen the initial echo and the end echo to get diameter of the head were considered to be too inaccurate. Therefore exclusively ultra sonic methods were used. If only A-scan equipment is used the most common ultrasonic method for determining the head diameter is the transmission method. In B-scan however the sum of the distances between the initial echo and the midline echo measured from both sides has been used. For the sake of comparison the same way was used for calculations also in A-scan together with th transmission method

Comparisons in the diameter of the head with the results of other authors were made by using the values obtained by A-scan at the age of three hours at test point P_2, with the scalp oedema excluded. This value was chosen for the following reasons 1) the diameter of the head at test point P_2 corresponds best with the biparietal diameter of the foetus used for the foetal cephalometric determinations (116) 2) the age of three hours corresponds best with the situation immediately after the delivery (how ever it has not been proved whether this valu correlates best with the head diameter just before the delivery) nd 3) the scalp oedema supposed to be lacking in the foetus The val are not, however entirely comparable w th t results of foetal cephalometry because the f biparietal diameter is determined as the dist ce from the outside of the proximal skull surfa e t the inside of the distal skull surface and the distance is not always corrected to corr pond with the true diameter of the head According to Pystynen *et al* (169) it seems more advisable to accept the diameter recorded than to m and arrive at the scorrect diameters by calculations when one is correlating the head diamet with the birth weight.

The oedema of the scalp As the oedema of the scalp was calculated as the difference in the distances from the initial echo to the end echo measured from each side, the presumption had to be made that the registration of the end echo would not affect the distances. As mentioned above, the determination of the end echo is rather inaccurate in B-scan (143) and therefore the scalp oedema was not calculated in B-scan.

The discrepancies between the end echoes may also be caused by the asymmetry of the skull as pointed out by Barrows *et al* (13) and Brown (28) This error which is due to the non homologous positioning of the transducer on both sides of the head (13) was excluded with the use of the scanning arm of the B-scan equipment also in A-scan It was thus made sure that the same plane was used not only for A-scan and B-scan examinations but also for the examinations performed from both the right and left side. However variations in the angle of inclination within the same plane cannot be excluded, which may affect the determination of the position of the end echo.

The position of the midline When the possible shift of the midline of the brain is determined its position is compared with its theoretical place, i e the midline of the skull These two midpoints may differ somewhat from each other also in healthy people as can be seen in the normal limits of the midline shift. When the midline of the skull is determined by using distances measured from the leading edge of the initial echo reasons causing differences in the thickness of the head wall such as scalp oedema, intracranial haematoma and variations in the thicknesses of the muscles or of the bone may lead to errors if not excluded (19 35 39 55 56 108) In the present study these factors are excluded.

The distance between the inner tables of the skull bones is not affected by the reasons mentioned above Therefore half of this distance will indicate the theoretical position of the mid line. The amount of the midline shift is thus half of the difference of th distances between the midline echo and the end echo on each side (28, 178) The above mentioned difficulties in determining the end echo will affect this method, too, when B-scan is used. Therefore the only way to determine the place of the midline in B-scan for comparison with A-scan results was to use the scalp oedema determined by A-scan also in B-scan calculations.

The temporal horn echo The possibility of determining the temporal horn echo for the calculation of the brain mantle index was discussed by Mostafawy (154) In his population of 400 children the BMI was measurable in 82 per cent of all children and in only a little more than 10 per cent in early infancy In the study by Dill (58) consisting of 311 children there were 65 infants under 12 months. No cases with an absent temporal horn echo were reported. In the present study an echo usually one with two peaks was observed approximately half way between the midline echo and the end echo in all infants at an examination from test point P_1

Between the temporal horn echo and the midline echo there was usually simultaneously another double echo This echo which was demonstrated to originate in the circumpedun cular cistern, was used as a point of reference when the temporal horn echo was looked for in A-scan and identified in the B-scan pictures *(Fig 3—6 8 and 10)*

A misinterpretation of the echo assumed to originate from the temporal horn may cause errors, making the brain mantle usually narrower than it really is, as pointed out by Schiefer *et al.* (178) The most obvious source of error in such cases is the echo of the Sylvian fissure which can be detected from test point P_1 (78 104 140 176, 195) In the present study the Sylvian fissure, recognized by the pulsations of the middle cerebral artery was observed to lie somewhat higher and somewhat more later ally than the temporal horn echoes, when the scanning was done along the ear vertical line (EVL)

Errors to the opposite direction, on the other hand may be caused, *e. g* by the echo from the circumpeduncular cistern. The obser vation was made that in newborn infants it was

not necessary to direct the ultrasonic beam somewhat downwards to find the temporal horn as recommended for adults by Schiefer *et al.* (178)

The method used in A-scan to calculate an index to describe the position of the temporal horn echo or the thickness of the brain mantle is not suitable for B-scan because of the inaccuracy of the end echo in B-scan as pointed out by Lombroso *et al.* (143) They used for the same purpose a ratio between the distance from the initial echo to the lateral wall of the ipsilateral trigone temporal horn complex and the head diameter measured externally with callipers. In the present study the distance from the initial echo to the contralateral temporal horn echo is used, because the contralateral temporal horn echo is easier to register and because the ipsilateral temporal horn echo often becomes part of the initial echo (178) The distance was divided by the head diameter measured ultrasonically instead of the calliper measurement by Lombroso *et al.* (143)

The echo of the body of the lateral ventricle Emery (51) reported that in the brain of a newborn the difference in th acoustical impedances between the ventricular fluid and the brain tissue seemed insufficient to produce an echo with the range of ultrasonic energy available to him. Many other authors have, however presented the opinion that t is possible to obtain echoes from the bodies of the lateral ventricles also in newborns (6 23 38 70 87 108 116 140, 153 154 183) According to Sjögren (181) the absorption coefficients for newborn infants may be expected to be lower than those for adults for both the skull and the cerebral tissue because of a lower calcium density and a lower degree of myelinisation, among other things. On the other hand the reflection capacity of the ventricular surface will also fall with a decreased density of the cerebral tissue

Jeppsson (108) and Sjögren (181) calculated that the bodies of the lateral ventricles can be visualized in children whose skull bone is not thicker than 3 mm by using a probe of 2 MHz. Lombroso *et al.* (143) suggested that infants have a more primitively shaped ventricular system, *i. e* a less complex orientation of ventricular walls with respect to the outer skull structures, which makes a more extensive visualization of the ventricular walls possible in various planes of B-scanning in this earlier stage of development.

In the present study the echo of the body of the lateral ventricle was identified by air injected into the ventricular system *(Fig 10 A—E)* If the echo assumed to be the echo of the body had originated in the tracts of myelinated nerves as suggested by Emery (51) a new echo would have come into sight more medially on the ipsilateral side after the injection of air Now only the original echo became first stronger and finally moved more laterally indicating that the echo originated in the ventricular wall. Mostafawy (154) examined 400 children and was able to determine the distance between the outer walls of the lateral ventricles in 80 per cent In early infancy the percentage was 100 per cent In the present study the visualization of the bodies was successful in all cases in A-scan and in all but one in B-scan in th 51 infants examined.

C. DISCUSSION OF THE RESULTS

The initial echo It was impossible to distinguish the different components of the initial echo complex either n A-scan or in B-scan. The only definable point of the initial echo complex was the first deflection in A-scan and the outer margin in B-scan. The initial point of these formations was therefore used for measurements. Multiple echoes in connexion with the initial echo (164 178) due to subgaleal haematoma or cephalhaematoma were not observed n the subjects examined.

The end echo Distel and Kasper (41) demonstrated in children showing no cerebral lesion a peak of small amplitude at a short distance from the end echo. It may originate at the interfaces of the subarachnoidal space. They found a high correspondence between the pneumoencephalographic measurements of the subarachnoidal

space and the ultrasonic measurements. Distances of more than 2 mm were regarded as pathological.

Oksala (162) pointed out that, analogous to the eye, the small echo preceding the end echo might be induced by the divergency of the sound beam beyond the near field which does not reach the opposite skull bone. In the present study the corresponding echo was often seen in A scan while it was impossible to separate this echo from the end echo complex in B-scan. This circumstance will be explained by the worse resolution in B-scan registration due to limitations in the spot size and the worse dynamic range especially on the storage tube. Consequently the distance from the initial echo to the end echo will be somewhat shorter in B-scan than in A-scan thus affecting also the determination of the head wall thickness (see later)

When performing foetal cephalometry by both A-scan and B-scan examinations Iannirruberto and Gibbons (95) suggested that the accuracy in their study was probably related to the use of B-scan rather than A scan and to the selection of an extremely low echo sensitivity to permit a faint linear display of the foetal skull. However in a study like the present one most attention was paid to the ventricular echoes. The gain setting needed for visualizing the echoes of the temporal horns and of the bodies of the lateral ventricles led to so strong end echoes that the determination of the initial point of the end echo became inaccurate. This is in agreement with the observations made by Lombroso et al (143). The echo arising at the interface between the skin and air on the opposite side of the skull could neither be determined with the gain setting needed for visualizing the ventricular echoes because of the reverberation echoes following the end echo (Fig 5 (and 8)

The midline echo On the basis of this study I can agree with those authors who have suggested that the midline echo may originate in several structures of the mid-sagittal plane (60 89 104 108 140 190 219) Lithander 139) pointed out that in newborn infants midline echoes can be recorded over large areas of the frontal temporal and parietal regions, e. g from third ventricle, septum pellucidum and cerebri, i. e within the entire area in whic probe can be applied almost perpendicul the sagittal plane of the skull. In the pr study an almost continuous line of midlin hoes was observed in B-scan recordings bet test points P_1 and P_2 corresponding to the poral and parietal regions *(Fig 4—6 and 8)*

Dilling and Feuerlein (40) suggested th was significantly more difficult to visualiz midline echo among the echoes of the m complex in infants and children than in y adults. In the present study it was easier to a distinct midline echo from test point P_2 from P_1 in A scan. In B-scan the echo line c midline echoes was broader in the upper corresponding to test point P_2 *(Fig 4—6 an* This indicates the better reflecting properti septum pellucidum compared to the sour the midline echo recorded from test poin which is the area usually used for mi determination by most authors. However significant difference was noticed in the d mination errors of the distance from the in echo to the midline echo between test poin and P_2 or between A scan and B-scan meth

The diameter of the head. The decrease in head diameter observed in the present s *(Fig 11 and 12)* is in agreement with the ob vation of Willocks et al. (225) They exam the biparietal diameter in 25 newborns by c per at short intervals after the delivery noticed that the diameter usually decrea during the first 24 hours of life. The change not related to the method of delivery In ano group of 38 newborn infants they could not any statistical change between the second sixth day of life. Kohorn (116) found a decr in the biparietal diameter measured by call in some cases, usually within the first six h after delivery Subsequent change during following 24 hours was found to be within error of the calliper measurements in this pop ation. Durkan and Russo (48) suggested t the variations in the biparietal diameter meas

ed by calliper during the first 48 hours were within the range of the observer error

According to Piiroinen and Manninen (165 166) the biparietal diameter measured by ultrasound was after vaginal delivery during the first 24 hours usually (in 67 6 %) smaller than the foetal biparietal diameter before delivery After a delivery by Caesarean section the change was smaller In the present study the decrease in the head diameter was constantly observed by all ultrasonic methods used. The decrease was equal at test points P_1 and P_2. On the contrary the increase in the head diameter between the ages of two and six days was significant only at test point P_2, corresponding approximately with the rate of growth in the foetal biparietal diameter during the last weeks of pregnancy (123 160 192, 228)

The reason for the changes in this transverse diameter of the head is obscure The decrease cannot result from the disappearing scalp oedema, because that was already excluded. In the present series there were only three deliveries by the Caesarean section. Also in them a corresponding decrease and increase in the head diameter was observed. Willocks *et al* (228) suggested that the decrease might be attributable to the effects of nursing with the baby lying on its side. More information might be received if the occipitofrontal diameter were measured simultaneously with the transversal diameter of the head

The linear regression equation between birth weight and the postnatal transversal diameter of the head in the present study *(Fig 13)* was statistically equal with that presented by Piiroinen and Manninen (165) Ojala *et al.* (160) have pointed out that when the biparietal diameter of the foetal head was correlated with the weight the foetuses in their series were heavier than foetuses elsewhere with the same biparietal diameter In the study by Pystynen *et al.* (169) the birth weight was almost always more than 2 500 g if the biparietal diameter exceeded 8.5 cm. In the present series two children out of 51 having a head diameter of more than 8.5 cm weighed less than 2 500 g at birth.

When the corresponding birth weights for the mean of the head diameter (91.8 mm) in the present study were calculated by using the equations presented by Hellman *et al* (86) Kohorn (116) Thompson (192) Kratochwil (123) Willocks *et al.* (228) Cohen (36) and Sabbagha *et al.* (172) the obtained values were 360—710 g lower than the mean in this study (3 490 g) The values given by Levi *et al* (137) for 591 newborns were on the average 240 g lower than those of the present study With the equations of Ojala *et al.* (160) and Pystynen *et al* (169) values 930—1 185 g higher were obtained The difference in the birth weights between the sample of Piiroinen and Manninen (165) and the present group was not more than 5 g Thus the head diameter of the newborn infants, according to Piiroinen and Manninen (165) and the present study is bigger in Southern Finland than in Northern Finland (160 169) as compared to the same birth weight.

The values of height at birth compared with those given by other Finnish authors were 1 7—2.0 cm lower in the present study calculated on the basis of the mean of the head diameter (91.8 mm)

The head circumference was also 0.6 cm smaller in the present study compared with the values given by Piiroinen and Manninen (165)

The thickness of the head wall. The anatomical measurements performed by Macdonald (146) without ultrasound gave for the parietal bone a thickness of just under 1 mm. Willocks *et al.* (228) reported the average thickness of 1.3 mm for the skull bone in the region of the parietal eminences and one of 1.2 mm for the scalp in infants weighing more than 2 500 g The values obtained by ultrasound for the head wall thickness in newborn infants have all been higher than those from the anatomical measurements both in the present study and in previous literature (38, 101 182) in spite of the apparent compression of thickness in the bony layer due to the higher sound velocity in bone 82 96)

As far as A-scan is concerned, the values of the thickness of the head wall in the present study *(Table 8)* agree with the value of

of septum pellucidum regardless of the side of examination. Otherwise the lateral ventricle index values did not differ significantly between A scan and B-scan, and they agreed well with values presented by Sjögren (182) Krijgsman (125) Mostafawy (154) and Dill (58) in A-scan Also values reported by West (217) calculated by using the inner diameter of the skull as divisor correspond well with those of the present study On the other hand, values presented by Brahme and Trågårdh (23) are only little more than half of the values presented by other authors. A statistical difference between the lateral ventricle indices of boys and girls, as suggested by Sjögren (182) was not observed in the present study in agreement with Krijgsman (125) The lateral ventricle index has not been used in B-scan by other authors The present study shows that it can be calculated in B-scan in the same way as in A-scan and that the lateral ventricle index values are as reliable in B-scan as in A-scan *(Table 15)*

Krijgsman (125) suggested that the higher thickness of septum pellucidum in newborns will explain the higher lateral ventricle index in them. The calculated *thickness of septum pellucidum* in the present study was, however on the average so small that it cannot explain alone the higher lateral ventricle index in newborns. The higher values in newborns can als explained as a phenomenon analogical witl reduction in the relative size of the ventri system during foetal life (132) still contin after birth.

Abnormal findings On the basis of brain tions Larroche and Baudey (133) describ cavum septi pellucidi in 18 out of 22 in born at term. Krijgsman (125) found a ca septi pellucidi in 24 out of 28 infants in age tween birth and 14 days. In the present s only one such case was found. On the c hand, it is obvious that the cavum does always extend to the coronal plane used in study or it may be so narrow that it cann identified by ultrasound.

As to other abnormal findings no diagno subdural bleeding was made during the pre study However as pointed out by several thors in A scan (12 71 139 164) and in B- (1 53) normal findings do not exclude possibility of a unilateral or bilateral subd haematoma Therefore the possibility of dural haematomas is not excluded echoe phalographically in the present study In of these restrictions I will completely agree Lahoda *et al* (129) recommending an echoe phalographic control for all newborns ha had difficulties during the delivery

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VIII SUMMARY

Purpose of the study The study was performed to find out the normal values and normal variations in the echoencephalographic examinations immediately after birth and during the first week of life. In addition, correlations between certain physical parameters of the newborn and the biparietal diameter of the head were calculated for comparison with results of other authors. Further the purpose was to investigate the applicability of B-scan in newborns and to compare the results with those of the A-scan technique.

Subjects and methods 51 healthy newborn infants weighing from 2 220 to 4 960 g at birth were examined seven times during the first week of life using both A-scan and B-scan. The examinations by both methods were performed immediately after each other at the ages of 3 6 12, and 24 hours and 2 4 and 6 days. In A-scan two test points along the ear vertical line were used for registration. Test point P_1 *(Fig 2)* just above the external auditive canal was used for the registration of the contralateral temporal horn echoes and test point P_2 4—5 cm from the horizontal line connecting margo infraorbitalis and the external auditive canal for the registration of the echoes of the bodies of the lateral ventricles. Test point P_2 was also used for determining the diameter of the head by the transmission method. In B-scan the coronal plane running along the ear vertical lines on each side was used To make sure that the same plane was used both in A-scan and in B-scan examinations, the scanning arms of the B-scan equipment were used also when registering the A-scan tracings. The A-scan tracings registered at test points P_1 and P_2 on each side and the head diameter measured by the transmission method were photographed on the same plate (*Fig 5*) The coronal scans in B-scan were registered separately from each side and stored for photographing on the upper and lower screens of the storage oscilloscope (*Fig 6*)

Certain distances *(Fig 7)* in the pictures were measured and the values obtained were used for calculations. The following distances and indices were calculated for both A-scan and B-scan, unless otherwise mentioned

— the diameter of the head
— the oedema of the scalp (only in A-scan)
— the thickness of the head wall
— the superficial structure index of Sjögren (181)
— the shift of the midline
— the thickness of the septum pellucidum
— the thickness of the brain mantle
— the brain mantle index (BMI) by Schiefer *et al* (177)
— the reciprocal brain mantle index by Dill (38)
— the contralateral temporal horn index (CTHI) by the present author (200)
— the common width of the bodies of the lateral ventricles
— the width of a single body of the lateral ventricle
— the lateral ventricl index by Sjögren (180)

The values obtained by A-scan and B-scan were compared with one another Within each method values obtained for different ages were compared. Also the values obtained for infants of primiparae and multiparae or for infants delivered vaginally in different p[illegible] were

compared with one another whenever they were relevant for such comparisons.

Results. A significant decrease in *the head diameter* was observed at both test points in both A-scan and B-scan echoencephalography as well as in the transmission method (performed only at P_2) during the first week of life. The lowest value was reached at the age of two days. Between the ages of two and six days a significant increase in the head diameter was observed at test point P_2 but not at P_1. The increase corresponded very well with the rate of growth reported for the foetal head during the last weeks of pregnancy. Reasons for these changes cannot be clarified on the basis of the present study.

The linear regression equations between certain physical parameters of the newborn and the biparietal diameter of the head gave the formulas, $y = (683 \pm 20)\,x - 2780$ for the birth weight, $y = (2.38 \pm 0.07)\,x + 26.91$ for the height at birth and $y = (2.23 \pm 0.05)\,x + 14.09$ for the occipitofrontal circumference of the head. The Pearsonian correlation coefficients (r) were 0.437 ± 0.128, 0.459 ± 0.130 and 0.516 ± 0.125 respectively (*Fig. 13, 14 and 15*).

The thickness of *the scalp oedema* varied between 0.9 and 1.5 mm during the whole week at test points P_1 and P_2.

The thickness of the head wall was at P_2 equal in A-scan and B-scan. At P_1 the head wall was observed to be significantly thicker in B-scan than in A-scan. The following explanation for the phenomenon is suggested. The echo described by Distel and Kasper (41) and assumed by them to originate at the interface of the subarachnoidal space will be incorporated in the end echo complex due to the worse resolution of the B-scan especially on the storage tube. This factor will explain also the other differences observed in the values calculated on the basis of the position of the end echo. The same variations as in the head wall thickness were observed also in the corresponding superficial structure indices.

The midline deviations did not differ significantly from one another in A-scan and in B-scan. Neither was there any significant difference between the shifts at test points P_1 and P_2 in the whole group. An almost significant difference in the midline shift was observed at test point P_2 both in A-scan and in B-scan at the ages of six and twelve hours in infants delivered vaginally in the cephalic presentation between the group having the left position and that having the right position in utero. As the difference was not found to be significant before the age of six hours, the oedema of brain rather than the moulding of the head seems to be the explanation for this difference, thus giving evidence for the fact that also in uncomplicated deliveries an inevitable transitory minimal brain trauma might happen.

A considerable amount of midline shifts of more than 2 mm was observed during the first week of life both in A-scan and in B-scan. It was calculated that within 99 per cent tolerance limits a midline shift of 3 mm cannot be considered pathological during the first week of life.

The brain mantle was on the average 1.3 mm thicker in A-scan than in B-scan due to the peculiarities of the end echo in B-scan. For the same reason the BMI expressed significantly higher values in B-scan as compared with A-scan. Consequently lower values were obtained for B-scan when the reciprocal BMI was calculated. When calculating the contralateral temporal horn index no significant difference was observed between A-scan and B-scan. It seems that, in spite of the thickness of the skull and scalp included in the distances used for calculating the value, this index is better suitable for B-scan than the other indices which depend on the accurate determination of the end echo.

The mean common width of *the bodies of the lateral ventricles*, the width of a single body and the lateral ventricle index did not show any statistical differences between A-scan and B-scan. Neither did the successive values during the first week of life differ statistically from the respective mean values. There were no statistical differences in the widths of the bodies of the lateral ventricles and in the lateral ventricle indices between infants of primiparae and multi-

parae No difference was observed to be caused by the different foetal position in utero during the delivery Neither was there any statistical difference between boys and girls.

One case with an obvious cyst of septum pellucidum was observed. The possibility of existing subdural haematomas cannot be excluded in the series on the basis of normal findings in echoencephalography

The mean values for various quantities in echoencephalography during the first week of life are summarized in *Table 16*

Table 16. Mea values for arious quantities in echoencephalography during the first week of life

	A-scan	B-scan
Head wall t P	4.6 ± 2.0 mm	3.6 ± 1 7 mm
t P	4.2 ± 1.8 mm	4.1 ± 1.8 mm
Brain mantle	18.2 ± 2.1 mm	16.9 ± 2.0 mm
Brain mantle index	2.28 ± 0.20	2.39 ± 0.21
Reciprocal BMI	0.44 ± 0.03	0.42 ± 0.03
Contralateral temporal horn index	0.748 ± 0.017	0.751 ± 0.015
Width of single body of the lateral entricle	14 4 ± 1.5 mm	14.4 ± 1.3 mm
Common width of the bodies	28.7 ± 2.3 mm	29.0 ± 2.1 mm
Lateral entricle index	0.313 ± 0.027	0.316 ± 0.025
dline shift at P	ad 3 mm	ad 3 mm
t P	ad 3 mm	ad 3 mm

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